BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

(12) UK Patent Application (19) GB (11) 2 297 089 (13) A

(43) Date of A Publication 24.07.1996

(21) Application No 9600963.4

(22) Date of Filing 17.01.1996

(30) Priority Data
(31) 9500076 (32) 17.01.1995 (33) ES

(71) Applicant(s)
Zeneca Farma S.A.

(Incorporated in Spain)

C/Josefa Valcárcel n°3y5, 1°, 28070 Madrid, Spain

(72) Inventor(s)
Andy J Barker
Antonio Monge Vega
Elizabeth Hamilton

(74) Agent and/or Address for Service
Boult Wade Tennant
27 Furnival Street, LONDON, EC4A 1PQ,
United Kingdom

(51) INT CL[6]
C07D 241/52 , A61K 31/495

(52) UK CL (Edition O)
C2C CAA CKB CKV CLW CLY CLZ CMB CMD CME CMF CMG CQS CRV CSC CSD CSN CYX C1434 C1562 C1614 C1628 C200 C213 C214 C22Y C220 C246 C247 C25Y C250 C252 C255 C28X C281 C29X C29Y C30Y C305 C31Y C311 C313 C314 C32Y C321 C322 C323 C328 C327 C328 C332 C334 C337 C338 C339 C34Y C340 C342 C350 C351 C352 C354 C355 C36Y C364 C366 C368 C37Y C373 C380 C385 C396 C397 C40Y C43X C440 C464 C51X C510 C511 C513 C52Y C524 C531 C55X C601 C613 C614 C62X C62Y C620 C621 C624 C625 C627 C628 C63Y C630 C634 C640 C65X C650 C652 C655 C657 C660 C661 C665 C667 C670 C671 C672 C675 C676 C678 C694 C698 C72Y C720 C740 C742 C744 C75Y C750 C754 C76X C775 C780 C80Y C802
U1S S1313

(56) Documents Cited
Chemical Abstracts 124:55903 Chemical Abstracts 123:340002 Chemical Abstracts 123:265

(58) continued overleaf

(54) **Cytotoxic quinoxaline 1,4-dioxides**

(57) Quinoxaline dioxide derivatives, some of which are novel compounds are useful as cytotoxic agents with selective activity in hypoxic cells, both in vitro and in vivo.

GB 2 297 089 A

13

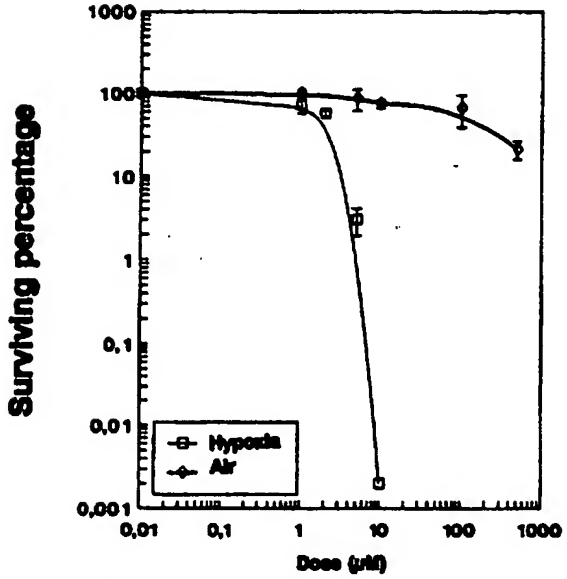


FIGURE 1A

27

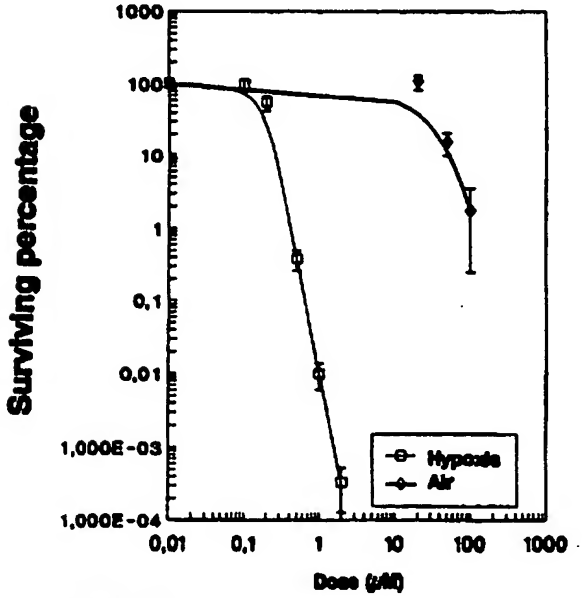


FIGURE 1B

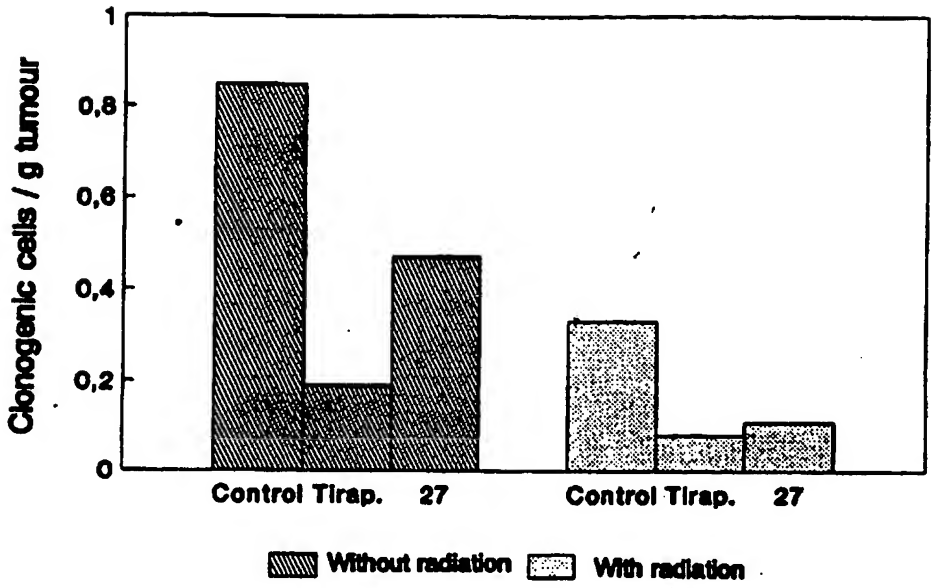

Clonogenic cells / g tumour
1
0,8
0,6
0,4
0,2
0
Control
Tirap.
27
Control
Tirap.
27
Without radiation
With radiation

FIGURE 2

DERIVATIVES OF QUINOXALINE 1,4-DIOXIDE PROCEDURE FOR THEIR PREPARATION AND THEIR EMPLOYMENT

This invention is referred to new derivatives of 1,4-quinoxaline dioxide, to procedures for their synthesis and their employment for the preparation of cytotoxic agents with selective activity in hypoxic cells, so much "in vitro" as "in vivo".

BACKGROUND ART

In the solid tumours there is an hypoxic cellular population (Moulder, J.E & Rockwell, S., Int.J.Radiat.Oncol.Biol.Phys.10:695/712,1984) that emerges because the vasculature of the tumour grows more slowly than the own tumour or because the chaotic growth of the tumoral mass can occlude partial or totally, in a permanent or transient way, the tumour vasculature. The existence of hypoxic cells in solid tumours has been demonstrated in animal tumours and in human tumour xenografts transplanted in immune deficient mice, and there are also data that support the hypothesis of their presence in human tumours (Vaupel, P. *et al.*, Cancer Res. 49:6449-6465, 1989).

In addition to be resistant to radiotherapy (Thomlinson, R.H. & Gray, L.H. Br.J.Cancer 9:539-549, 1955), hypoxic cells can be also resistant to quimiotherapy due to their non proliferative state, and to be located beyond the diffusion distance of some compounds. However, there is a group of antitumoral agents, called bioreductive agents, which have been designed with the idea of using the hypoxia conditions of some tumour cells to obtain a therapeutic benefit, due to the fact that the non tumoral cells are normally well oxygenated (Adams, G.E. et al., Biochem. Biophys. Res. Comm., 72:824-829, 1976). The bioreductive agents are compounds that are converted in cytotoxic species through reduction (bioreductive activation), mechanism that it is favored at low oxygen concentrations. Among this group of compounds,

derivatives of 1,2,4-benzotriazine 1,4-dioxides stand out, that, in addition to be more toxic in hypoxia, possess activity as anticancer agents (Brown, J.M. & Lemmon, M.J., Cancer Res., 50:7745-7749, 1990). An important compound of this type is SR 4233 (Tirapazamine), currently in clinic phase, which is described and recovered with other derivatives in the Patent USA 5.175.287 as well as in the Patent WO 8908647. In the requests of the Patent WO 8802366 and of the Patent WO 9104028 various derivatives of Tirapazamine are described.

Tirapazamine (3-amino-1,2,4-benzotriazine 1,4-dioxide) is the cytotoxic agent which is activated by reduction and that, to date, has demonstrated to be more selective "in vitro" (HCR= 75 in V79 cells). However, it shows a low potency and scarce solubility in water.

Previously, derivatives of quinoxaline 1,4-dioxides had not been evaluated as cytotoxic selective agents in hypoxia. In Cihak, R. and Vontorkova, M., Mutat. Res., 144 (2): 81-84 (1985), cytogenetic effects of various quinoxaline 1,4-dioxides are described. In Davis, C.D. et al., Cancer Lett., 73 (2-3): 95-104 (1993), mutagenic effects of heterocyclic amines, more specifically of quinoxaline N-oxides, are described. In Nunoshiba, T. and Nishioka, H., Mutat. Res., 217 (3): 203-209 (1989), some quinoxaline 1,4-dioxides with genotoxic activity in *Escherichia coli* and *Salmonella typhimurium*, are described. In Usui, T., Chem. Abst., 94 (21): 167640m (1981) quinoxaline 1,4-dioxides that contain in their structure a group 5-nitro-2-furyl and have antitumoral activity, are described. In Ley and Seng, Synthesis, 415-422 (July, 1975) it is described the preparation of 2-(3-dimethylamino-propylamino)-quinoxaline-1,4-dioxide. In Seng, F. and Ley, K., Angew.Chem. 11, 1010-1011, it is described the preparation of 4-cyano-7,8-dimethyl-2-oxo-1,24-oxadiazole [2,3-a] quinoxaline 5-oxide as intermediate in lumichrome synthesis. In the German Patent request 2232468 the preparation of 4-cyano-5-oxide-2-oxo-1,2,4-oxadiazolo[2,3-a]quinoxaline from 3-amino-2-quinoxalinecarbonitrile 1,4-dioxide and fosgene in chlorobenzene at 90° C is described. In the German Patent 2255946

the preparation of various ureas from 1,2,4-oxadiazol[2,3-3,4]benzo-1,2,4-triazine by treatment with primary and secondary amines, is described; these products were tested for bactericidal activity.

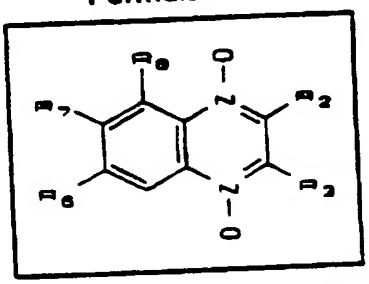
In the US Patent request 4343942 the preparation and trial as antimicrobial agents and promoters of animal growth of 6,7 replaced 3-amino-2-quinoxalinecarbonitrile 1,4-dioxide.

DESCRIPTION OF THE INVENTION

The present invention is referred to derivatives of quinoxaline 1,4-dioxides that have demonstrated to be selective cytotoxic agents in hypoxia conditions. Some of the compounds are 100 times more potent, 4 times more selective, at least 10 times more soluble in water and with better therapeutic in vivo index than SR 4233.

The most of the compounds are of new synthesis.

Formula I



Wherein R_2 is cyano or C(1-4)alkyl, $-CH_2$-NH-NH-COO-C(1-4)alkyl, C(1-4)alkyloxycarbonyl, C(1-4)alkylthio, C(2-5)alkanoyl, C(1-4)alkyl-O-CO-C(1-4)alkyl or a group of formula -C(X) =Y-Z wherein X is H or C(1-4)alkyl, Y is CH or N and, Z is benzoyl optionally mono- or di- substituted with halogen, C(2-5)alkanoyl or phenylamino optionally mono- or di- substituted with NO_2.

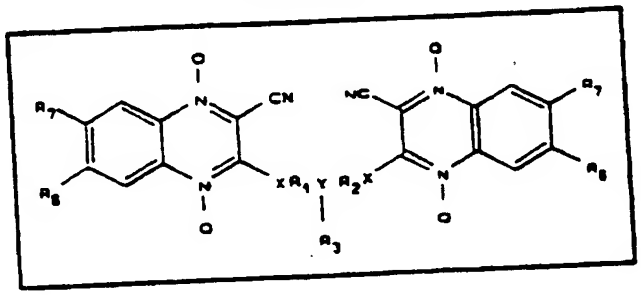
Wherein R_3 is H; amino optionally mono- or di- substituted with C(1-4)alkyloxycarbonyl; C(2-5)alkanoylamino optionally substituted on carbon with halogen; phenylthio, phenylsulfinyl or phenylsulfonyl optionally mono- di- or tri-substituted on phenyl with halogen or NO_2; a group of formula -NH-C(1-6)alkyl-N(A1)(A2) wherein A1 and A2 are independently H or C(1-4)alkyl, or A1 and A2 together complete a 5 or 6 membered heterocyclic ring optionally containing a N, O or

S atom in lieu of a carbon atom; C(2-6)alkanoylamino; C(2-6)alkanoyl; hydroxy; mercapto; C(1-4)alkoxy; aryloxy; C(1-4)alkylthio; C(1-4)alkylsulfinyl; C(1-4)alkylsulfonyl; C(1-4)alkyloxycarbonyl; halogen; C(1-6)alkyl; a group of formula -NH-CO-Het wherein Het is a 5 or 6 membered heterocyclic ring containing one atom of O or S; C(1-4)alkylsulfonylamino; C(1-4)alkylsulfinylamino; C(1-6)alkylamino optionally substituted on carbon with OH, SH or halogen; arylamino; a group of formula -N(A1)(A2) wherein A1 and A2 are C(1-4)alkyl, or A1 and A2 together complete a 5 or 6 membered heterocyclic ring optionally containig a N, O or S atom in lieu of a carbon atom.

In this report the term "aryl" such and as here is indicated includes aromatic rings of 5 or 6 members, with or without heteroatoms as N, S or O, and they can have or not 1, 2, or 3 substituents as halogen; nitro; sulfo; alkyl (1-6 C); alkoxy (1-6 C); carboxy; alkoxycarbonyl; cyano; carbamoyl; formyl.

R_6 and R_7 independently represent H; halogen; C(2-5)alkanoyl; CF_3; C(1-4)alkyl; C(1-4)alkoxy; C(1-4)alkylthio; C(1-4)alkylsulfinyl; C(1-4)alkylsulfonyl; C(2-5)alkanoylamino; cyano; cyclohexyl optionally substituted with 1-2 substituents selected from NO_2 and C(1-4)alkyl; phenyl optionally substituted with 1-2 substituents selected from NO_2 and C(1-4)alkyl; R_8 represents H or NO_2.

Formula II



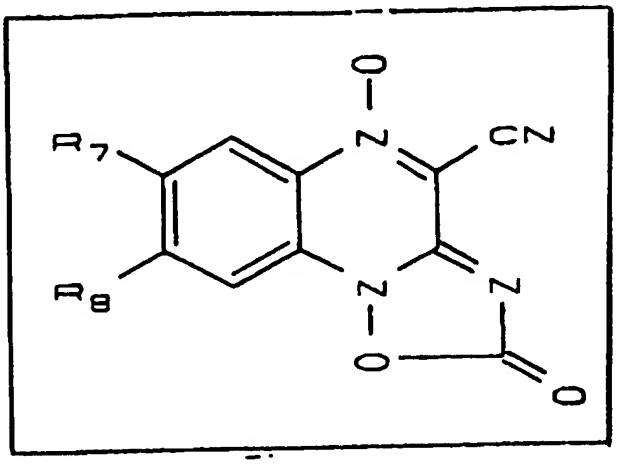
X can be N, O or S. Y can be N, O, S or C.

R_1, R_2 and R_3 are alkylic chains (1-4 C).

R_6 and R_7 independently represent H; halogen; C(2-5)alkanoyl; CF_3; C(1-4)alkyl; C(1-4)alkoxy; C(1-4)alkylthio; C(1-4)alkylsulfinyl; C(1-4)alkylsulfonyl; C(2-

5)alkanoylamino; cyano; cyclohexyl optionally substituted with 1-2 substituents selected from NO_2 and C(1-4)alkyl; phenyl optionally substituted with 1-2 substituents selected from NO_2 and C(1-4)alkyl; R_8 represents H or NO_2.

Fórmula III



R_7 and R_8 independently represent H; halogen; C(2-5)alkanoyl; CF_3; C(1-4)alkyl; C(1-4)alkoxy; C(1-4)alkylthio; C(1-4)alkylsulfinyl; C(1-4)alkylsulfonyl; C(2-5)alkanoylamino; cyano; cyclohexyl optionally substituted with 1-2 substituents selected from NO_2 and C(1-4)alkyl; phenyl optionally substituted with 1-2 substituents selected from NO_2 and C(1-4)alkyl.

Some particular quinoxalines of the invention are represented in the Figure I in which:

R_2 is cyano, C(1-4)alkylthio, C(2-5)alkanoyl or a group of formula -C(X) =Y-Z wherein X is H or C(1-4)alkyl, Y is CH or N and, Z is benzoyl optionally mono- or di-substituted with halogen, C(2-5)alkanoyl or phenylamino optionally mono- or di-substituted with NO_2.

R_3 is acylamino such as acetamido, 2-chloroacetamido or C(1-4)alkyl.

R_6 and R_7 independently represent H; halogen; C(2-5)alkanoyl; CF_3; C(1-4)alkyl; C(1-4)alkoxy; C(1-4)alkylthio; C(1-4)alkylsulfinyl; C(1-4)alkylsulfonyl; C(2-5)alkanoylamino; cyano; cyclohexyl optionally substituted with 1-2 substituents selected from NO_2 and C(1-4)alkyl; phenyl optionally substituted with 1-2 substituents selected from NO_2 and C(1-4)alkyl; R_8 represents H or NO_2.

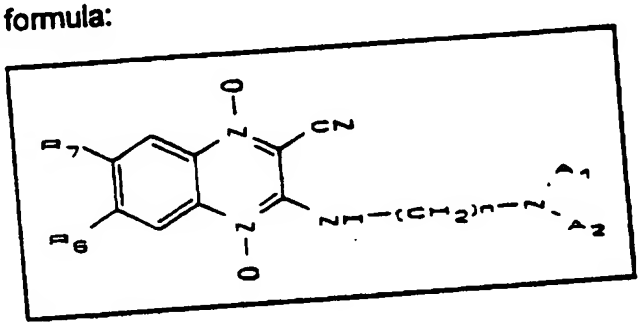
Some preferred quinoxalines of the invention are represented in the Formula I in which:

R_2 is cyano.

R_3 is hydrogen; C(1-4)alkyl; chloro; prymary amino (NH_2); C(1-4)alkylamino optionally substituted on carbon with hydroxy, mercapto or halogen; -N(A1)(A2) wherein A1 and A2 are C(1-4)alkyl, or A1 and A2 together complete a 5 or 6 membered heterocyclic ring optionally containing a N, O or S atom in lieu of a carbon atom.

R_6 and R_7 independently represent H; halogen; C(2-5)alkanoyl; CF_3; C(1-4)alkyl; C(1-4)alkoxy; C(1-4)alkylthio; C(1-4)alkylsulfinyl; C(1-4)alkylsulfonyl; C(2-5)alkanoylamino; cyano; cyclohexyl optionally substituted with 1-2 substituents selected from NO_2 and C(1-4)alkyl; phenyl optionally substituted with 1-2 substituents selected from NO_2 and C(1-4)alkyl; R_8 represents H or NO_2.

Specially preferred quinoxalines of the invention are represented in the following structural formula:



Where n may be 0-4, preferably 2 or 3. A_1 and A_2 are independently hydrogen, C(1-4)alkyl, optionally replaced the alkyl by hydroxy, C(1-4) alkoxy, amino, C(1-4) alkylamino, thiol or C (1-4) alkylthio; A1 and A2 together complete a 5 or 6 membered heterocyclic ring optionally containing a N, O or S atom in lieu of a carbon atom; the heterocyclic ring may be optionally replaced a carbon by C(1-4) alkyl.

R_6 and R_7 independently represent H; halogen; C(2-5)alkanoyl; CF_3; C(1-4)alkyl; C(1-4)alkoxy; C(1-4)alkylthio; C(1-4)alkylsulfinyl; C(1-4)alkylsulfonyl; C(2-5)alkanoylamino; cyano; cyclohexyl optionally substituted with 1-2 substituents

selected from NO_2 and C(1-4)alkyl; phenyl optionally substituted with 1-2 substituents selected from NO_2 and C(1-4)alkyl; in positions 5 and 8 may be H or NO_2.

All the compounds may be in the form of some of the pharmaceutically acceptable salts, and they are prepared in a conventional method, such as by reaction of the free base in an adecuate solvent, for example diethyl ether, acetone or methanol, with a solution containing an equivalent of the acid wished in a adequate solvent, for example diethyl ether, acetone or methanol. The salt precipitates in the solution or is recovered by evaporation of the solvent. Pharmaceutically acceptable salts include for example, hydrochloric, hydrobromic, sulfate, oxalate, citrate, tosylate, mesylate. Also, sodium, potasium, calcium salts or from organic salts such as caffeine, ethylamine, lysine.

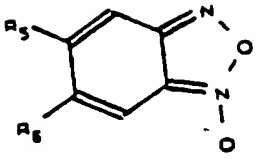
A quinoxaline of the invention may be administered to animal of hot blood, including to the man, in the form of a pharmacological composition that contains the quinoxaline associated with a solvent or pharmacologically acceptable vehicle.

The quinoxalines of the invention are selectively toxic for hypoxic cells, so they are intended to be used in combination with other treatments more toxic for well oxygenated cells. They can be administered before and/or after radiation, in a regimen of fractionated radiotherapy. They could also be used in combination with other cytotoxic drugs such as alkylating agents, or other antitumoral drugs with different mechanism of action.

The composition may be in a form adapted for its oral administration, such as pills or capsules, or, specially, for parenteral injection, as a solution, suspension or sterile emulsion.

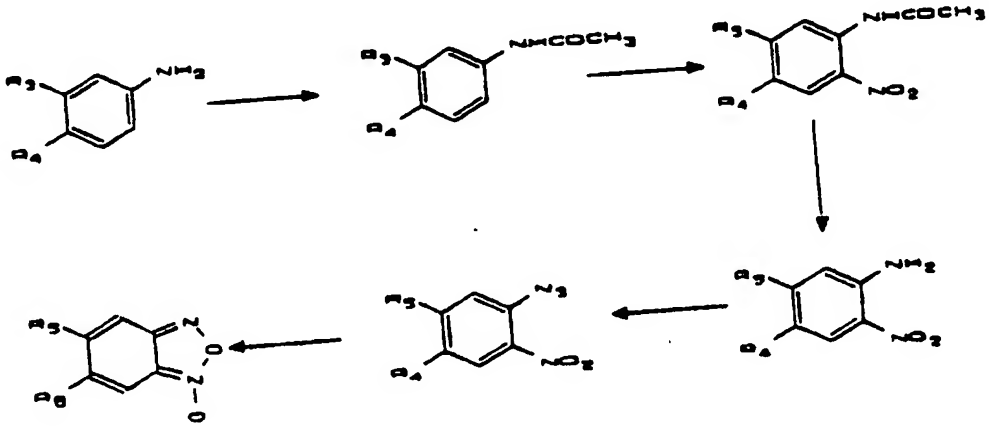
MODES OF CARRYING OUT THE INVENTION

General method for the preparation of 3-amino-2-quinoxaline carbonitrile 1,4-dioxide derivatives. The compounds are prepared starting with the benzofuroxanes of formula:



by Beirut reaction. The benzofuroxanes are prepared starting from the corresponding anilines by acylation in acetic anhydride/acetic acid and then, nitration of the corresponding amides by using nitric acid and sulfuric acid. Hydrolysis of substituted acetamides give the substituted 2-nitroanilines which are diazotated and treated with sodium azide. Displacement by azido group and subsecuent cyclocondensation of the 2-nitroazide in boiling toluene afford the benzofuroxanes. Scheme 1. The general pathway for this synthesis has been described previously (Fitton, A.O., Smalley, R.K. In: Practical Heterocyclic Chemistry, 57-61, Academic Press. London and New York (1968)).

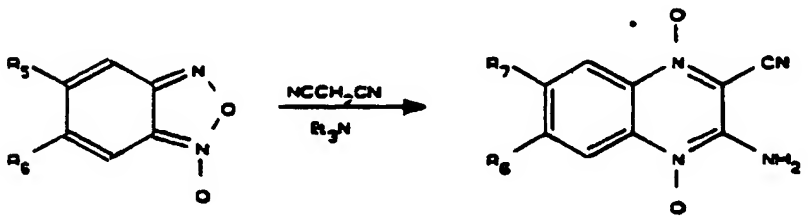
Scheme 1



Beirut reaction by using malononitrile in the presence of an appropiate condensing base, such as triethylamine, give the 6 and/or 7 substituted 3-amino-2-quinoxalinecarbonitrile 1,4-dioxides (Ley, K. and Seng, F. Synthesis 415-422 (1975)). Scheme 2. (Examples 1-8). The benzofuroxane starting material is not symmetric with respect to its own 5 and 6 positions (which are the 6 and 7 positions of the resulting quinoxaline 1,4-dioxides). Therefore, a mixture of the 6- and 7-substituted materials

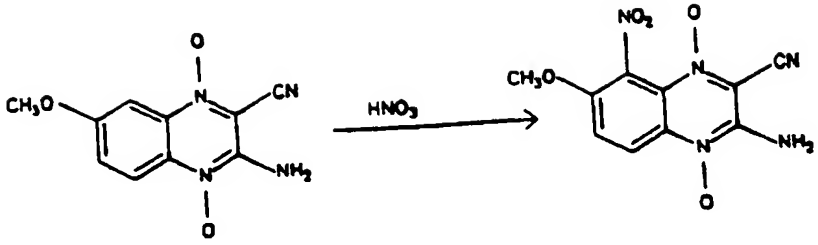
may result. In general, Beirut reaction mainly affords the 7 isomer (Cheeseman, G.W.H. and Cookson, R.F., Condensed pyrazines, John Wiley and Sons Eds., 35: 36-37 (1979)) (Mason, J.C. and Tennant, G., J. Chem. Soc. Chem. Commun., 586 (1971)). If desired, this mixture can be separated using conventional means.

Scheme 2



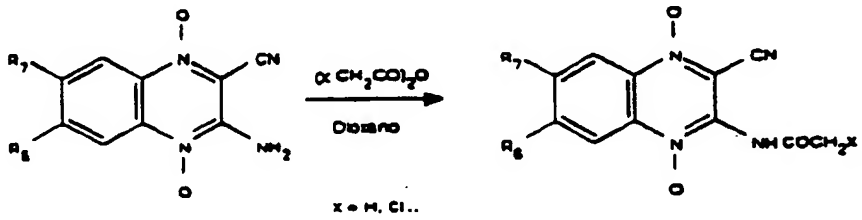
Nitration of 3-amino-7-methoxy-2-quinoxalinecarbonitrile 1,4 dioxide at room temperature for 10 h affords the 8-nitro derivative. Scheme 3. (Example 9).

Scheme 3



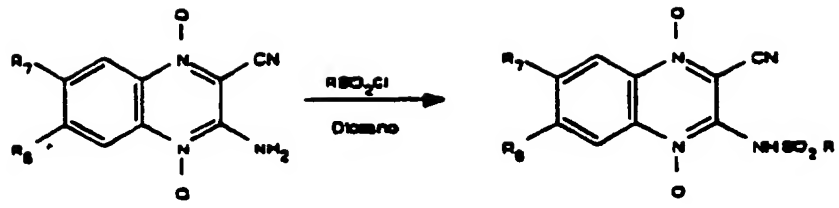
Reaction of 3-amino-2-quinoxalinecarbonitrile 1,4-dioxides with anhydrides in an appropiate dry non protic solvent, yield the corresponding amides in position 3. Scheme 4. (Examples 10 and 11).

Scheme 4



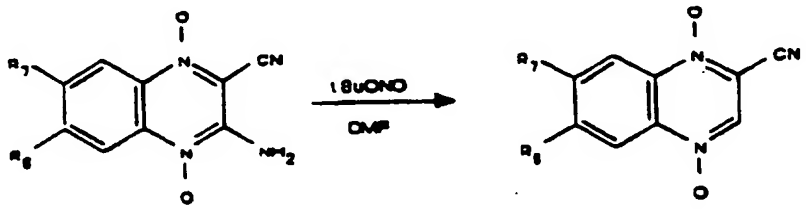
In addition reaction with sulfonyl chloride in an appropiate dry solvent such as dioxane, afford the corresponding alkylsulfonylamines and arylsulfonylamines in position 3. Scheme 5. (Example 12).

Scheme 5



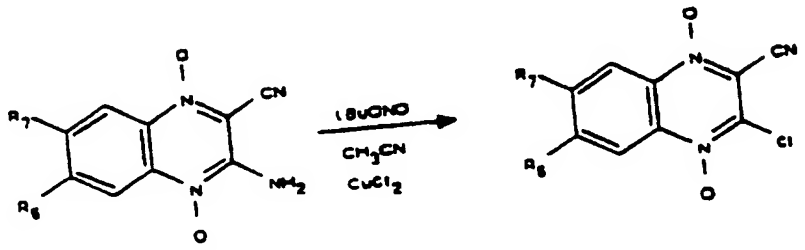
Diazonium salt formation starting with 6 and/or 7 substituted 3-amino-2-quinoxalinecarbonitrile 1,4-dioxides and tert-butylnitrite at 60-100 °C, and replacement by hydrogen in the presence of an hydrogen donor solvent, such as N,N-DMF, yield 2-quinoxalinecarbonitrile 1,4-dioxide derivatives. Scheme 6. (Examples 13-19).

Scheme 6



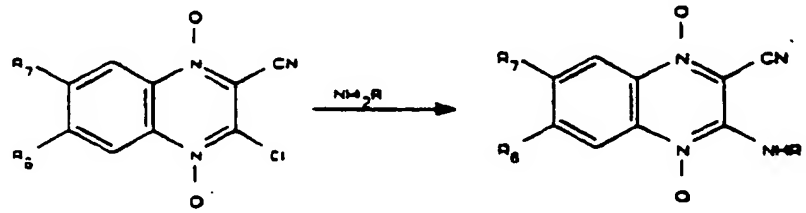
Replacement of the diazonium salt by halogen in the presence of X_2Cu, in an appropiate solvent, such as acetonitrile, afford the corresponding 6 and/or 7 substituted 3-chloro, 3-bromo and 3-fluoro-2-quinoxalinecarbonitrile 1,4-dioxides. Scheme 7. (Examples 20-25).

Scheme 7



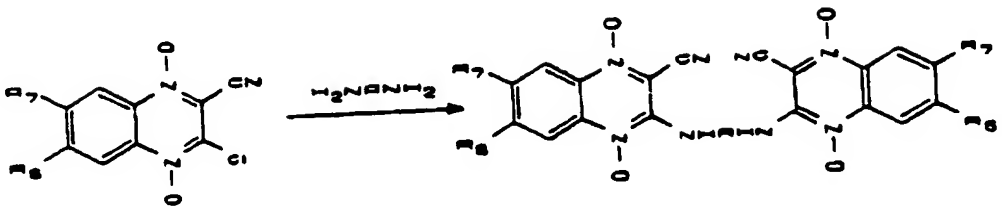
Replacement of the halogen in position 3 of the quinoxaline ring by using several amines in an appropiate solvent at 5-100 °C, afford the 6 and/or 7 substituted 3-(N,N-dialkylamino)alkylamino, 3-alkylamino and 3-arylamino-2-quinoxalinecarbonitrile 1,4-dioxides. Scheme 8. (Examples 26-39).

Scheme 8



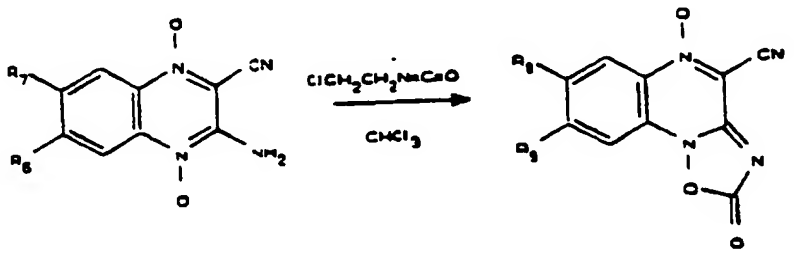
Reaction of the 3-chloro compounds with a diamine affords a quinoxaline dimer. Scheme 9. (Example 40).

Scheme 9



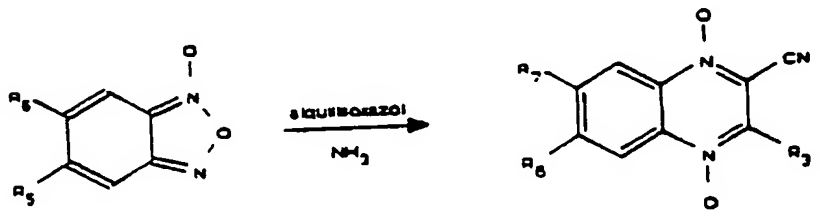
Treatment of 6 and/or 7 substituted 3-amino-2-quinoxalinecarbonitrile 1,4-dioxide with 2-chloroethylisocyanate in the presence of an appropiate dry solvent, such as dioxane or toluene, at 90-150 °C give 7 and/or 8 substituted 4-cyano-2-oxo-1,2,4-oxadiazolo[2,3-a]quinoxaline 5-oxide (Seng, F. and Ley, K. Angew. Chem. internat. Edit. Vol. 11, Nº 11 (1972)). Scheme 10. (Examples 41 and 42).

Scheme 10



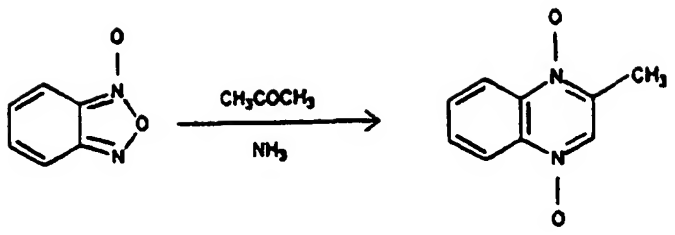
Reaction of 5 and/or 6 substituted benzofuroxanes with 5-alkylisoxazole in ammonia atmosphere gives 6 and/or 7 substituted 3-alkyl-2-quinoxalinecarbonitrile 1,4-dioxide. Scheme 11. (Example 43).

Scheme 11



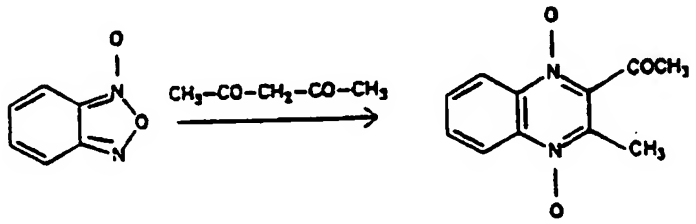
Beirut reaction between benzofuroxanes and ketones has been described previously; thus, benzofuroxane reacts with acetone in the presence of ammonia giving 2-methylquinoxaline 1,4-dioxide in good yield (Monge, A. et al., Ann. Quim., 71: 248 (1975)). Scheme 12. (Example 44).

Scheme 12



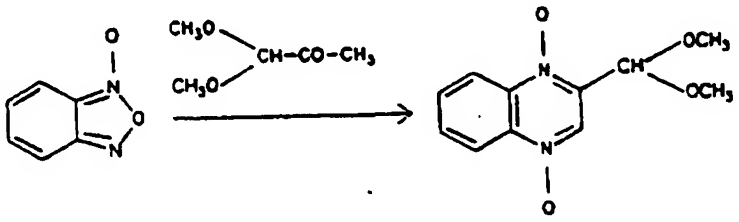
With acetylacetone provides 2-acetyl-3-methylquinoxaline 1,4-dioxide (Issidorides et al., J. Org. Chem., 31: 4067 (1966)). Scheme 13. (Examples 45-48).

Scheme 13



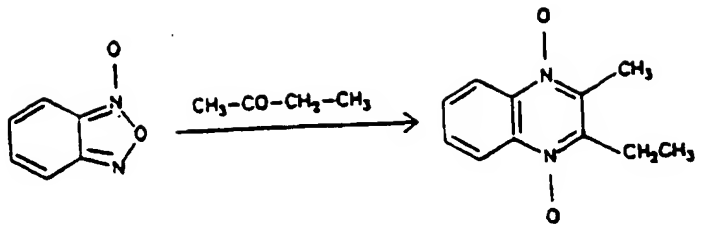
With pyruvaldehyde dimethylacetal gives 2-dimethoxymethylquinoxaline 1,4-dioxide (Johnston, Pfizer, Inc., Ger. Offen. 1927-337, C.A. 72, 11753 c). Scheme 14. (Examples 49 and 50).

Scheme 14



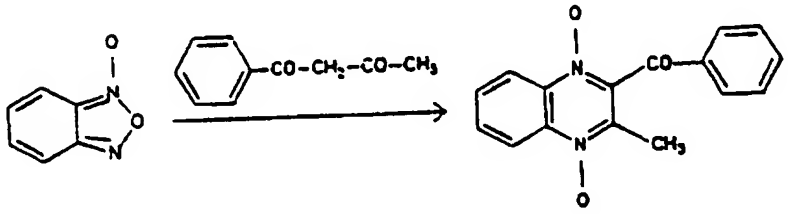
Reaction with butanone gives 2,3-dimethylquinoxaline 1,4-dioxide (Landkist, J. J. Chem. Soc., 2822 (1953)). Scheme 15. (Example 51).

Scheme 15



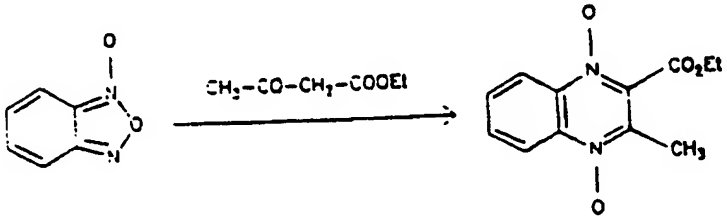
Reaction with benzoylacetone yields 2-benzoyl-3-methylquinoxaline 1,4-dioxide (Haddadin et al., Tetrahedron, 32: 719 (1976)). Scheme 16. (Example 52).

Scheme 16



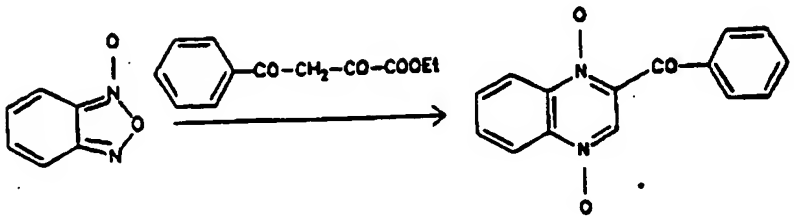
With ethyl acetoacetate yields 2-ethoxycarbonyl-3-methylquinoxaline 1,4-dioxide (Issidorides et al., J. Org. Chem., 31: 4067 (1966)). Scheme 17. (Example 53).

Scheme 17



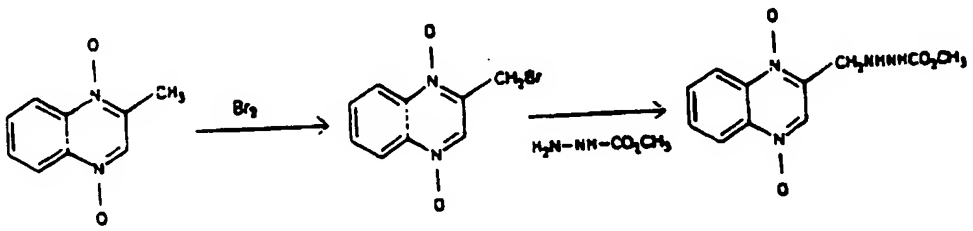
With ethyl benzoylpyruvate affords 2-benzoylquinoxaline 1,4-dioxide. Scheme 18. (Example 54).

Scheme 18



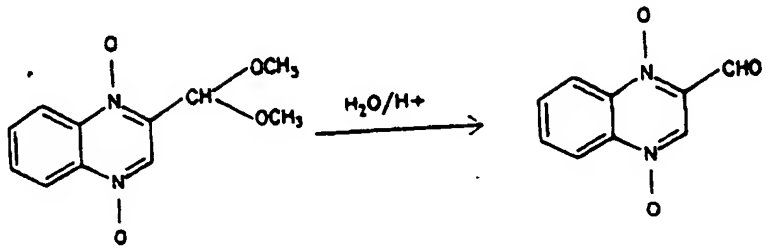
Bromination in acetic media of 2-methylquinoxaline 1,4-dioxide affords the bromomethyl analogue (Elina. Khin. Geterotsike Soedin. 72: 263 (1967)), which reacts with methylcarbazate by nucleophilic displacement of the bromine. Scheme 19. (Example 44).

Scheme 19



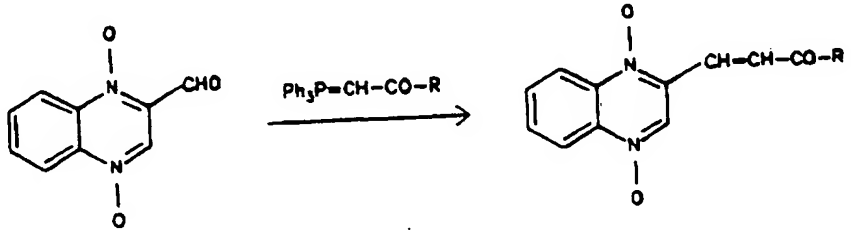
2-Formylquinoxaline 1,4-dioxide is obtained by hydrolysis of the acetal 2-dimethoxymethylquinoxaline 1,4-dioxide. Scheme 20. (Examples 49 and 50).

Scheme 20



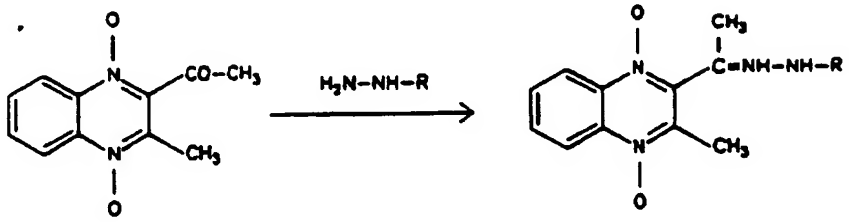
Wittig reaction between the formyl group and the corresponding iluro affords 2-(3-alkyl/aryl-3-oxo-1-propenyl)quinoxaline 1,4-dioxides. Scheme 21. (Examples 49 and 50).

Scheme 21



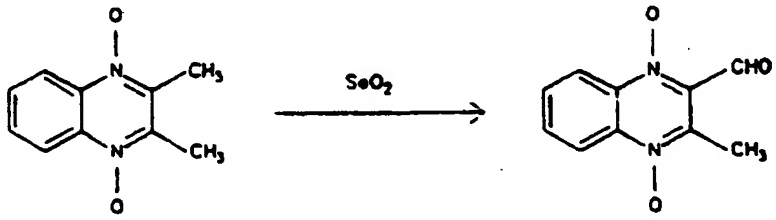
Condensation of 2-acetyl-3-methylquinoxaline 1,4-dioxide with hydrazines and hydrazides gives the imino derivatives. Scheme 22. (Examples 45-48).

Scheme 22



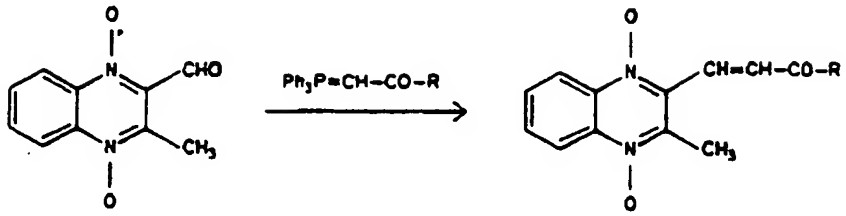
Selective oxidation of 2,3-dimethylquinoxaline 1,4-dioxide with selenium dioxide provides 2-formyl-3-methylquinoxaline 1,4-dioxide. Scheme 23. (Example 51).

Scheme 23



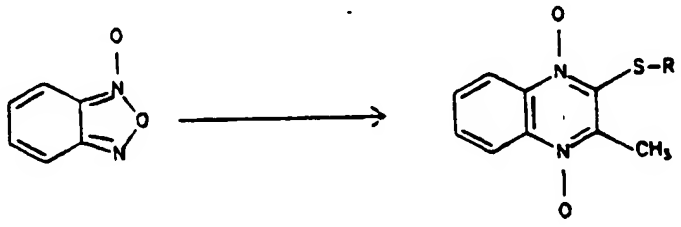
This reacts with yluros by Wittig condensation giving α,ß-insaturated ketones. Scheme 24. (Example 51).

Scheme 24



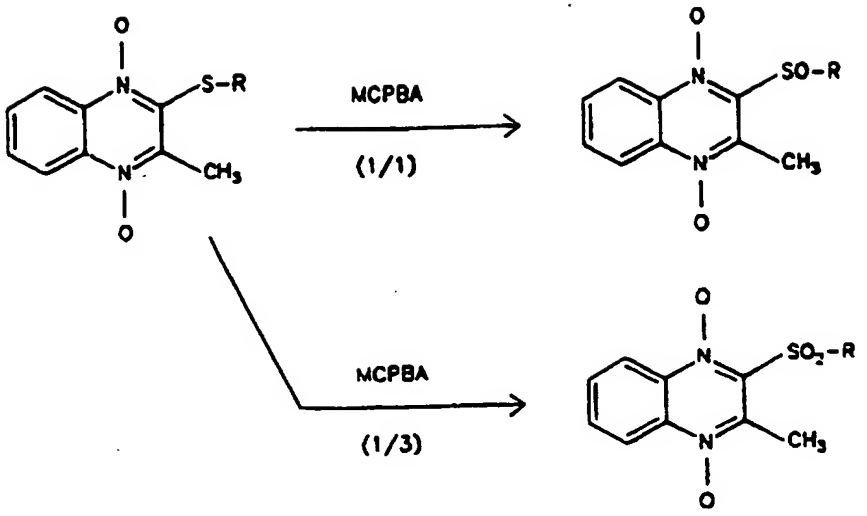
Reaction between benzofuroxanes and alkyl/arylthioacetones yields 2-methyl-3-alkyl/arylthioquinoxaline 1,4-dioxides (Abushanab, E., J. Org. Chem. 38: 3105-3107 (1973)). Scheme 25. (Examples 55, 58 and 59).

Scheme 25



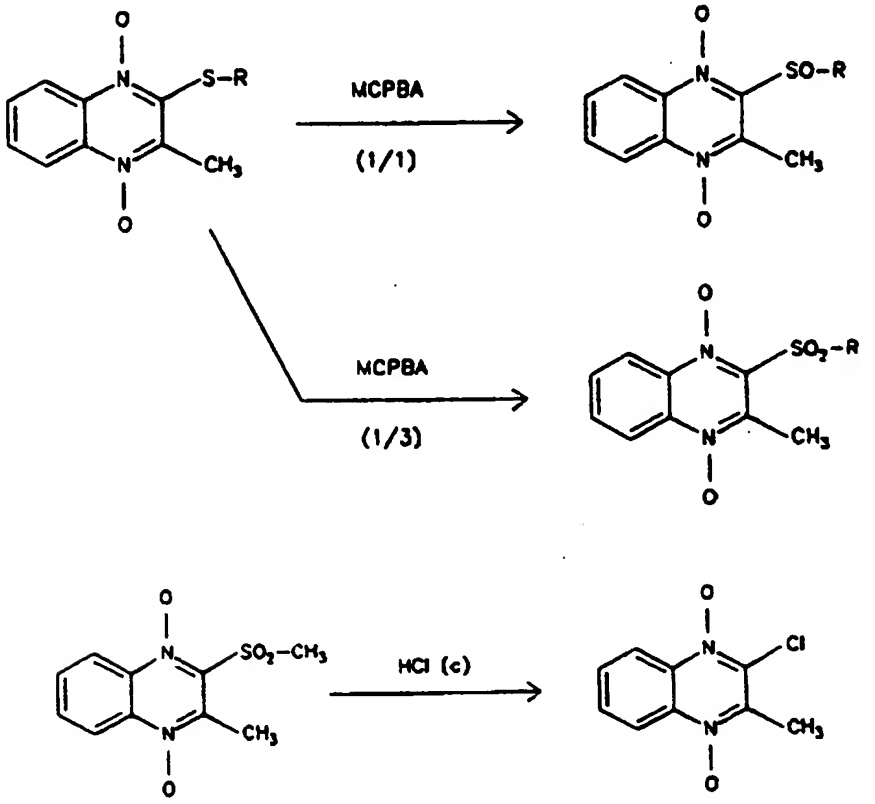
Selective oxidation of 2-methyl-3-alkyl/arylthioquinoxaline 1,4-dioxides with m-chloroperbenzoic acid (MCPBA) gives the corresponding sulfinyl (1:1 quinoxaline/MCPBA) and sulfonyl (1:3 quinoxaline/MCPBA) derivatives. Scheme 26. (Examples 56, 57, 60 and 61).

Scheme 26



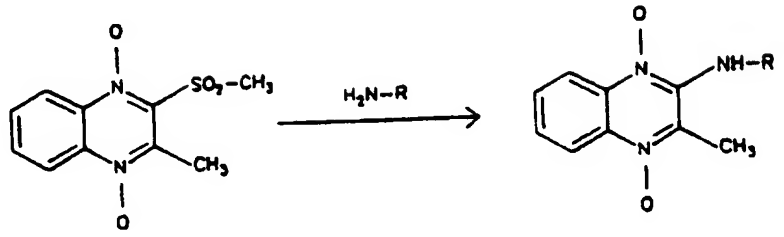
Nucleophilic replacement of the sulfonyl group by chlorine in concentrated HCl gives the corresponding 2-chloroquinoxaline 1,4-dioxide. Scheme 27. (Example 62).

Scheme 27



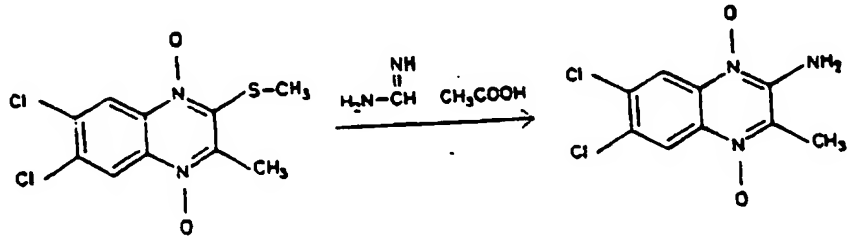
Replacement of the sulfonyl group by amines affords the 2-amino derivative. Scheme 28. (Example 63).

Scheme 28



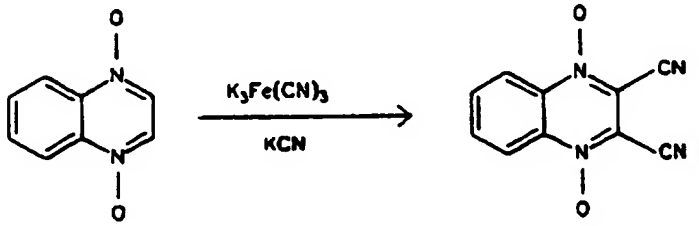
Reaction between 6,7-dichloro-2-methyl-3-methylthioquinoxaline 1,4-dioxide and formamidine acetate in 2-ethoxyethanol as solvent affords 2-amino-6,7-dichloro-3-methylquinoxaline 1,4-dioxide. Scheme 29. (Example 64).

Scheme 29



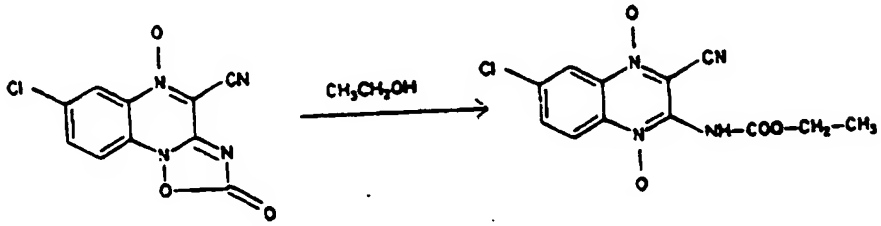
Treatment of quinoxaline 1,4-dioxide with potassium ferricyanide and potassium cyanide in ethanol-water produces 2,3-dicyanoquinoxaline 1,4-dioxide (Kobayashi, Y et al., J. Org. Chem., 37: 3588-3591 (1972)). Scheme 30. (Example 65).

Scheme 30



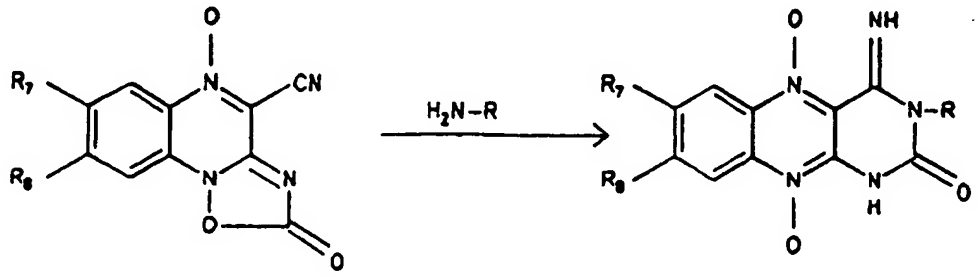
7-Chloro-4-cyano-2-oxo-1,2,4-oxadiazolo[2,3-a]quinoxaline 5-oxide reacts with ethanol giving 3-ethoxycarbonylamino-7-chloro-2-quinoxalinecarbonitrile 1,4-dioxide. Scheme 31. (Example 66).

Scheme 31



Reaction of 4-cyano-2-oxo-1,2,4-oxadiazolo[2,3-a]quinoxaline 5-oxides with ammonia and primary amines yields the cyclocondensation to benzopteridine 5,10-dioxide (Seng, F. and Ley, K., Angew. Chem. internat. Edit. 11: 1009-1011 (1972)). Scheme 32. (Examples 66 and 67).

Scheme 32



The invention is described with reference to the drawings of which:

Fig 1A and 1B are graphs of percentage surviving cells after treatment with an increasing dose of an active ingredient and

Fig 2 is a graph of clonogenic cells per g tumour after treatment with an active ingredient, with or without radiation.

EXAMPLES

The following examples further illustrate the compounds of the invention and methods for synthesizing and using them, and are not intended to limit the invention in any manner.

Experimental: Melting points were determined using a Mettler FP82+FP80 apparatus and are uncorrected. Elemental analyses were obtained from vacuum-dried samples (over phosphorous pentoxide at 3-4 mm Hg, 24 hours at about 60-80 °C). Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR apparatus, using potassium bromide tablets for solid products and sodium chloride plates for liquid products; the waves numbers are expressed in cm^{-1}. The ^{1}H-NMR spectra were obtained on a Brucker AC-200E (200 MHz) instrument, with tetramethylsilane as the internal reference, at a concentration of about 0.1 g/mL and with dimethylsulfoxide-d_6, chloroform-d, trifluoracetic acid (TFA) and D_2O as the solvents; the chemical shifts are reported in ppm of tetramethylsilane in δ units. The mass spectra were recorded on a Hewlett-Packard 5988-A instrument at 70 eV.

Thin layer chromatography (TLC) was carried out on silica gel (HF, 254-266, Merck or DSF-s, Cammaga) with the indicated solvents and the plates were scanned under ultraviolet light at 254 and 366 nm. Column chromatography was carried out with silica gel 60 Merck (70-230 mesh ASTM) and indicated solvents.

Analyses indicated by the symbols of the elements or functions were within ±0.4% of theoretical values. In the cases where the deviation is higher, the composition of the element deviated is indicated.

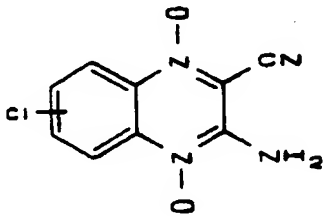
5-Chloro-4-fluoro-2-nitroaniline, 4-trifluoromethoxyaniline, 4-trifluoromethyl-2-nitroaniline, benzofuroxane, 5-chlorobenzofuroxane, 5-fluorobenzofuroxane, 5-methoxybenzofuroxane were purchased from Maybridge.

3,4-Dichloroaniline, 4,5-dimethyl-2-nitroaniline, 4-methyl-2-nitroaniline, 4,5-difluoro-2-nitroaniline, 3-chloro-4-methoxyaniline, 4-aminobiphenylo, tert-butyl nitrite, copper (II) chloride, chloroacetic anhydride, acetic anhydride, 2-chloroethylisocyanate, sulfonyl chlorides, acetonitrile, 3-(N,N-dimethylamino)propylamine, 2-(N,N-diethylamino)ethylamine, 2-(N,N-dimethyl)ethylamine, 4-(3-aminopropyl)morpholine, N-methyl-N,N-di-(3-aminopropyl)amine, 5-methylisoxazole, acetylacetone,

pyruvaldehyde dimethylacetal, benzoylacetone, ethyl acetoacetate, methylcarbazate, m-chloroperbenzoic acid, formamidine acetate were purchased from the Aldrich Chemical Company. Malononitrile from Lonza. N,N-Dimethylformamide, triethylamine, K_2CO_3, CH_2Cl_2, dioxane, toluene, methanol, acetone, acetic acid, nitric acid, concentrated HCl, concentrated sulfuric acid, sodium azide, butanone, selenium dioxide, chloroacetone, potassium cyanide, potassium ferricyanide, 2-ethoxyethanol, phenylhidrazine, 2,4-dinitrophenylhidrazine, thiosemicarbazide, p-toluensulphonylhidrazine, p-methoxy acetophenone, acetophenone, p-nitroacetophenone were purchased from Panreac.

EXAMPLE 1

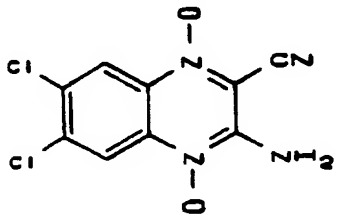
Preparation of 3-amino-6(7)-chloro-2-quinoxalinecarbonitrile 1,4-dioxide



A mixture of 5-chlorobenzofuroxane (10 mmol) and malononitrile (10.6 mmol) was stirred at 0 °C (ice-bath) for 10 min. A solution of triethylamine (5 drops) in N,N-DMF (3mL) was added dropwise. The mixture was stirred at room temperature for 24 h. and was filtrated. The crude solid was washed with diethyl ether (72 %). The mixture of 6 and 7 chloro isomers was purified by flash chromatography. Firstly 3-amino-7-chloro-2-quinoxalinecarbonitrile 1,4 dioxide was eluted with ethyl acetate (62 %), mp 263-264 °C. IR (KBr) 3433-3295, 2236, 1336 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 7.92 (d, 1 H, H_6, J= 9.0 Hz), 8.14 (s, 2 H, NH_2), 8.23-8.29 (m, 2 H, H_5 H_8). MS (EI) m/e (70 eV) M^+= 236. ANAL (calc. for $C_9H_5ClN_4O_2$) C,45,66; H,2,11; N,23,68. Found: C,45,82; H,2,11; N,23,82. The 6-chloro isomer was eluted with toluene:acetic acid (TDA) (10 %), mp 260 °C. ^1H NMR (dimethylsulfoxide-d_6) 8.00 (d, 1 H, H_7, J= 8.2 Hz), 8.32 (s, 3 H, NH_2 H_5), 8.33 (d, 1 H, H_8). MS (EI) m/e (70 eV) M^+= 236.

EXAMPLE 2

Preparation of 3-amino-6,7-dichloro-2-quinoxalinecarbonitrile 1,4-dioxide



A) Preparation of 5,6-dichlorobenzofuroxane

5 Steps are required for the synthesis of this benzofuroxane:

1) Preparation of 3,4-dichloroacetanilide

A mixture of 3,4-dichloroaniline (8.91 g, 55 mmol), acetic anhydride (8 mL) and acetic acid (8 mL) was heated under reflux for 15 min. The mixture was poured into ice-water and the resulting precipitate was filtered and dried at 60 °C in vacuo. The acetanilide was used without further purification.

2) Preparation of 4,5-dichloro-2-nitroacetanilide

8.98 g (44 mmol) of 3,4-dichloroacetanilide was added over a cooled (0 °C) mixture of 60% nitric acid (20 mL) and concentrated sulfuric acid (20 mL). After stirring at 0 °C for 10 min the mixture was allowed to reach the room temperature. The solution was poured into crushed ice and the precipitate filtered and dried at 60 °C in vacuo.

3) Preparation of 4,5-dichloro-2-nitroaniline

4,5-Dichloro-2-nitroacetanilide (8.71 g, 35 mmol) was used without further purification. It was heated in concentrated sulfuric acid (30 mL) at 100 °C for 15 min. The reaction mixture was allowed to cool and poured into crushed ice. The resulting solid was filtrated, washed with water and dried in vacuo at 60 °C. It was used without further purification.

4) Preparation of 4,5-dichloro-2-nitrophenylazide

Powdered 4,5-dichloro-2-nitroaniline (3.52 g, 17 mmol), concentrated HCl (20 mL) and water (60 mL) were stirred at room temperature for 5 min. The mixture was cooled at 0 °C and a solution of sodium nitrite (2 g, 29 mmol) in water (10 mL) was added. The insoluble material was discarded and the clear solution was treated with an aqueous solution of sodium azide (2.5 g, 38 mmol) and sodium acetate (50 g, 0.60 mol). The resulting solid was filtrated and dried in vacuo at 20 °C. CAUTION!: Azides should not be heated.

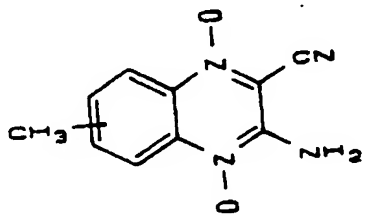
5) Preparation of 5,6-dichlorobenzofuroxane

A mixture of 4,5-dichloro-2-nitrophenylazide (2.33 g, 10 mmol) and toluene (25 mL) was heated under reflux for 2 h. After removal of the solvent a brown solid was obtained and used without further purification.

B) According to the procedure described in EXAMPLE 1. (48 %), mp 265 °C. IR (KBr) 3281, 2230, 1367 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 8.43 (s, 2 H, NH_2), 8.49 (s, 1 H, H_8), 8.53 (s, 1 H, H_5). MS (EI) m/e (70 eV) M^+= 270. ANAL (calc. for $C_9H_4Cl_2N_4O_2$) C,39.85; H,1.48; N,20.66. Found: C,40.08; H,1.48; N,20.39.

EXAMPLE 3

Preparation of 3-amino-6(7)-methyl-2-quinoxalinecarbonitrile 1,4-dioxide



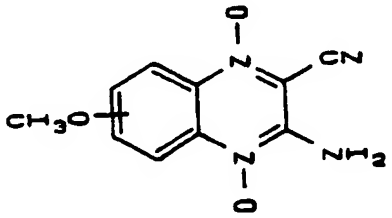
A) Preparation of 5-Methylbenzofuroxane

4-Methyl-2-nitrophenylazide and 5-methylbenzofuroxane were prepared starting from commercial 4-methyl-2-nitroaniline as described in EXAMPLE 2 and were used without further purification.

B) According to the procedure described in EXAMPLE 1. (52 %), mp 245-247 °C. IR (KBr) 3415-3330, 2233, 1332 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 2.49 (s, 3 H, CH_3), 7.48 (d, 1 H, H_7 6 isomer, J= 8.8 Hz), 7.73 (d, 1 H, H_6 7 isomer, J= 8.7 Hz), 7.96 (s, 2 H, NH_2 6 isomer), 8.05 (s, 2 H, H_5 6(7) isomers), 8.11 (s, 2 H, NH_2 7 isomer), 8.16 (d, 2 H, H_8 6(7) isomers, J= 8.7 Hz). MS (EI) m/e (70 eV) M^+= 216. ANAL (calc. for $C_{10}H_8N_4O_2$) C,55.56; H,3.70; N,25.92. Found: C,55.52; H,3.73; N,25.90.

EXAMPLE 4

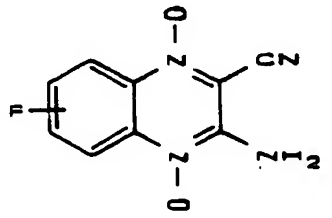
Preparation of 3-amino-6(7)-methoxy-2-quinoxalinecarbonitrile 1,4-dioxide



According to the procedure described in EXAMPLE 1. (40 %), mp 248-249 °C. IR (KBr) 3336, 2230, 1337 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 3.92 (s, 3 H, OCH_3), 7.48 (d, 1 H, H_7 6 isomer, J= 8.8 Hz), 7.73 (d, 1 H, H_6 7 isomer, J= 8.7 Hz), 7.96 (s, 2 H, NH_2 6 isomer), 8.05 (s, 2 H, H_5 6(7) isomers), 8.11 (s, 2 H, NH_2 7 isomer), 8.16 (d, 2 H, H_8 6(7) isomers, J= 8.7 Hz). MS (EI) m/e (70 eV) M^+= 216. ANAL (calc. for $C_{10}H_8N_4O_2$) C,55.56; H,3.70; N,25.92. Found: C,55.52; H,3.73; N,25.90.

EXAMPLE 5

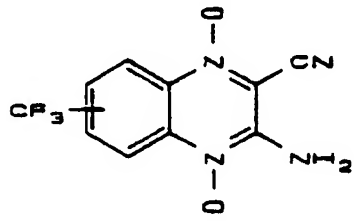
Preparation of 3-amino-6(7)-fluoro-2-quinoxalinecarbonitrile 1,4-dioxide



According to the procedure described in EXAMPLE 1. Mainly the 7 isomer was obtained (61 %), mp >300 °C. IR (KBr) 3340, 2230, 1378 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 7.81-7.89 (m, 1 H, H_6), 8.00 (s, 1 H, H_8), 8.05 (s, 2 H, NH_2), 8.29-8.36 (m, 1 H, H_5). MS (EI) m/e (70 eV) M^+= 220. ANAL (calc. for $C_9H_5FN_4O_2$) C,49.09; H,2.27; N,25.45. Found: C,48.91; H,2.34; N,25.23.

EXAMPLE 6

Preparation of 3-amino-6(7)-trifluoromethyl-2-quinoxalinecarbonitrile 1,4-dioxide



A) Preparation 5-trifluoromethylbenzofuroxane

1) Preparation of 4-trifluoromethyl-2-nitrophenylazida

Powdered 4-trifluoromethyl-2-nitroaniline (3.50 g, 17 mmol), concentrated HCl (20 mL) and water (60 mL) were stirred at room temperature for 5 min. The mixture was cooled at 0 °C and a solution of sodium nitrite (2 g, 29 mmol) in water (10 mL) was added. The insoluble material was discarded and the clear solution was treated with an aqueous solution of sodium azide (2.5 g, 38 mmol) and sodium acetate (50 g, 0.60 mmol). The oil was extracted with ethyl acetate (4 x 50 mL) and the organic layer dried over Na_2SO_4. After removal of the solvent at room temperature a clear oil was obtained and used without further purification.

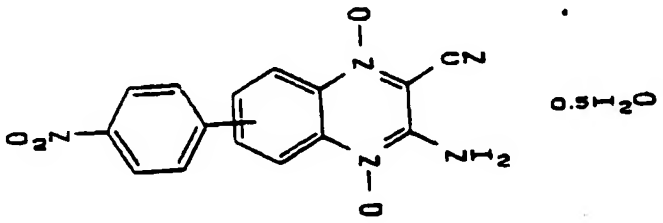
2) Preparation of 5-trifluoromethylbenzofuroxane

4-trifluoromethyl-2-nitrophenylazida (2.20 g, 9.4 mmol) was dissolved in toluene and the yellow solution was added dropwise over boiling toluene. After refluxing for 4 h and removal of the solvent a yellowish solid was obtained and used without further purification.

B) According to the procedure described in EXAMPLE 1. (55 %), mp 259-260 °C. IR (KBr) 3399-3282, 2230, 1346 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 7.96 (d, 1 H, H_7, 6 isomer, J= 8.9 Hz), 8.24 (d, 1H, H_6 7 isomer, J= 8.9 Hz), 8.47 (s, 4 H, NH_2 6(7) isomers), 8.53-8.56 (m, 4 H, H_5 H_8 and isomers). MS (EI) m/e (70 eV) M^+= 270. ANAL (calc. for $C_{10}H_5F_3N_4O_2$) C,44.45; H,1.85; N,20.74. Found: C,44.29; H,1.78; N,20.65.

EXAMPLE 7

Preparation of 3-amino-6(7)-(4-nitrophenyl)-2-quinoxalinecarbonitrile 1,4-dioxide, hemihydrate



A) Preparation of 5-(4-Nitrophenyl)benzofuroxane

1) Preparation of 4-phenylacetanilide

4-Aminobiphenylo (10 g, 59 mmol) and acetic anhydride (20 mL) were stirred and heated at 100 °C for 2 h. After cooling at 20 °C the mixture was poured into crushed ice and the white solid filtrated and used without further purification.

2) Preparation of 2-nitro-4-(4-nitrophenyl)acetanilide

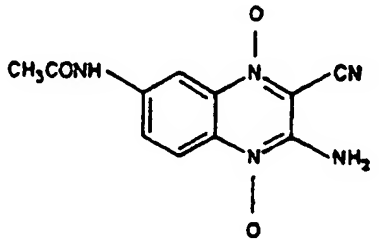
4-Phenylacetanilide (8.30 g, 39 mmol), 60% nitric acid (20 mL) and concentrated sulfuric acid (4 mL) were heated at 100 °C for 2 h. The mixture was allowed to stand at room temperature and was poured into crushed ice. The solid was filtrated and dried (60 °C in vacuo).

2-nitro-4-(4-nitrophenyl)aniline, 2-nitro-4-(4-nitrophenyl)phenylazide and 5-(4-nitrophenyl)benzofuroxane were prepared as described in EXAMPLE 1 and were used without further purification.

B) According to the procedure described in EXAMPLE 1. (22 %), mp 225 °C. IR (KBr) 3384-3257, 2231, 1343 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 7.64-8.53 (m, 7 H, ArH). MS (EI) m/e (70 eV) M^+= 323. ANAL (calc. for $C_{15}H_9N_5O_4 \cdot 0.5\ H_2O$) C,54.22; H,3.01; N,21.08. Found: C,54.14; H,2.95; N,20.96.

EXAMPLE 8

Preparation of 7-acetamido-3-amino-2-quinoxalinecarbonitrile 1,4-dioxide

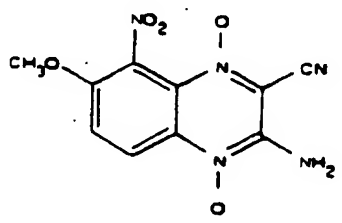


A) 4-Acetamido-2-nitroaniline was prepared starting from 2-nitro-1,4-phenylendiamine by controlled acetylation. The corresponding azide and benzofuroxane were prepared in the usual fashion as described in EXAMPLE 2.

B) According to the procedure described in EXAMPLE 1. IR (KBr) 3386-3257, 2235, 1341 cm^{-1}; ^1H NMR (dimethylsulfoxido-d_6) δ 2.11 (s, 3 H, CH_3); 7.89 (s, 2 H, NH_2); 7.92 (d, 1 H, H_6, J = 9.3 Hz); 8.22 (d, 1 H, H_6); 8.77 (s, 1 H, H_8); 10.52 (s, 1 H, NH). MS (EI) m/e (70 eV) M^+= 259. Anal. (calc for $C_{11}H_9N_5O_3$) C, 43.32; H, 2.55; N, 25.27. Found C, 43.49; H, 2.60; N, 25.09.

EXAMPLE 9

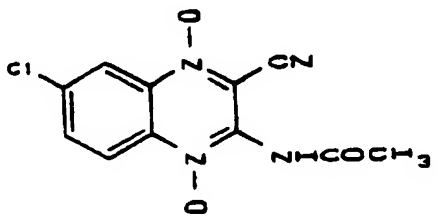
Preparation of 3-amino-7-methoxy-8-nitro-2-quinoxalinecarbonitrile 1,4-dioxide



A mixture of 3-amino-7-methoxy-2-quinoxalinecarbonitrile 1,4-dioxide (2.00 g, 8.62 mmol) and 60% HNO_3 was stirred at room temperature for 10 h. The solution was neutrallized with aqueous $HNaCO_3$ and extracted with ethyl acetate (5 x 100 mL). The organic layer was dried over Na_2SO_4. After removal of the solvent a red solid was obtained. Flash chromatography was carried on by eluting with a gradient of toluene/ethyl acetate. Finally, the product was recrystallized from ethyl acetate and dried in vacuo at 100 °C (P_2O_5) (18%); IR (KBr) 3441-3247, 2236, 1544, 1339 cm^{-1}; ^1H NMR (dimethylsulfoxide-d_6) δ 4.04 (s, 3 H, CH_3O); 8.02 (d, 1 H, H_6, J = 9.8 Hz); 8.13 (s, 2 H, NH_2); 8.44 (d, 1 H, H_5). MS (EI) m/e (70 eV) M^+= 277. Anal. (calc. for $C_{10}H_7N_5O_5$) C, 50.96; H, 3.47; N, 27.02. Found C, 50.55; H, 3.58; N, 26.64.

EXAMPLE 10

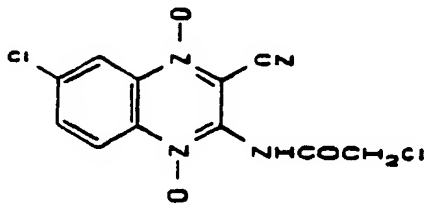
Preparation of 3-acetamido-7-chloro-2-quinoxalinecarbonitrile 1,4-dioxide



A mixture of 3-amino-7-chloro-2-quinoxalinecarbonitrile 1,4-dioxide (1.29 g, 5.40 mmol), acetic anhydride (15 mL) and concentrated sulfuric acid (1 mL) was stirred and heated at 90 °C for 25 min. The solution was poured into ice-water (100 g). The resulting precipitate was filtered off and washed with water. Recrystallization from N,N-DMF afforded orange crystals which were washed with diethyl ether (43%), mp 229-230 °C. IR (KBr) 3268, 2230, 1702, 1600, 1366, 1325, 739 cm^{-1}.^1H NMR (dimethylsulfoxide-d_6) 2,30 (s, 3 H, CH_3), 8.14 (m, 1 H, H_6), 8.50-8.55 (m, 2 H, H_5+H_8), 11,30 (s, 1 H, NH). MS (EI) m/e (70 eV) M^+= 278. ANAL (calc. for $C_{11}H_7ClN_4O_3$) C, 47.40; H, 2.51; N, 20.11. Found: C, 47.32; H, 2.49; N, 20.05.

EXAMPLE 11

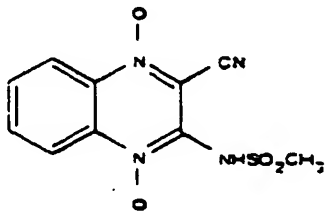
Preparation of 7-chloro-3-chloroacetamido-2-quinoxalinecarbonitrile 1,4-dioxide



Excess chloroacetic anhydride was added over a mixture of 3-amino-7-chloro-2-quinoxalinecarbonitrile 1,4-dioxide (0.75 g, 3.20 mmol) and dried dioxane (20 mL). The suspension was stirred at room temperature for 30 min. The precipitated solid was collected and washed with toluene (25 mL) and light petroleum ether (25 mL) (39%), mp 155 °C. IR (KBr) 3223, 2197, 1708, 1329, 675 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 4.57 (s, 2 H, CH_2CO); 8.10 (m, 1 H, H_5); 8.50 (m, 2 H, H_6 H_8); 11.6 (s, 1 H, NH). MS (EI) m/e (70 eV) M_+-35= 278. ANAL (calc. for $C_{11}H_6Cl_2N_4O_3$) C, 42.17; H, 1.92; N, 17.89. Found: C, 42.50; H, 2.07; N, 17.96.

EXAMPLE 12

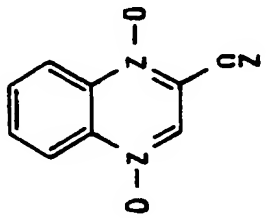
Preparation of 3-methylsulfonylamino-2-quinoxalinecarbonitrile 1,4-dioxide



A complete mixture of 3-amino-2-quinoxalinecarbonitrile 1,4-dioxide (1.00 g, 4.90 mmol), methanosulfonyl chloride (0.59 g, 0.15 mmol), $NaHCO_3$ (1.00g, 12,00 mmol) and dry dioxane (20 mL) was stirred at room temperature for 48 h. The solid was collected and washed with diethyl ether. Recrystallization from dioxane afforded 0.54 g (39 %), mp 255-256 °C. IR (KBr) 3413-3325, 2228, 1360 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 3,49 (s, 3 H, CH_3), 7.38-7.43 (m, 1 H, H_6); 7.70-7.74 (m, 3 H, NH, H_5, H_7); 8.12 (d, 1 H, H_8). MS (EI) m/e (70 eV) M^+= 280. ANAL (calc. for $C_{10}H_8N_4O_4S$) C, 42.85; H, 2.85; N, 20.00. Found: C, 43.25; H, 2.93; N, 20.11.

EXAMPLE 13

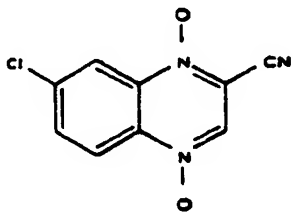
Preparation of 2-quinoxalinecarbonitrile 1,4-dioxide



Dry N,N-DMF (60 mL) was stirred and heated at 65 °C under nitrogen atmosphere. 3-Amino-2-quinoxalinecarbonitrile 1,4-dioxide (2.30 g, 11.39 mmol) was added. Tert-butyl nitrite (4 mL) was added, and following the addition an effervescence was observed (approx. 10 min) giving a dark brown solution. Additional tert-butyl nitrite (3 mL) was injected with a needle, appearing effervescence. The mixture was stirred and heated at 70 °C for 15 min, after removal of the solvent a dark waxy solid was obtained. Flash chromatography (toluene/ethyl acetate 100/13) gave a yellow solid which was recrystallized fron ethyl acetate to give yellow crystals (26 %), mp 195 °C. IR (KBr) 3012, 2240, 1369 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 8.03 (m, 2 H, H_6, H_7); 8.48 (d, 2 H, H_5, H_8, J=4.4); 8.91 (s, 1 H, H_3). MS (EI) m/e (70 eV) M^+= 187. ANAL (calc. for $C_9H_5N_3O_2$) C, 57.75; H, 2.67; N, 22.46. Found: C, 58.07; H, 2.71; N, 22.16.

EXAMPLE 14

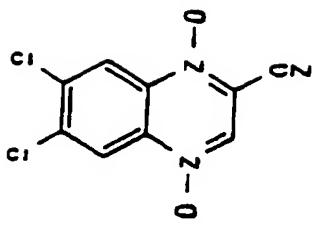
Preparation of 7-chloro-2-quinoxalinecarbonitrile 1,4-dioxide



Dry N,N-DMF (45 mL) was stirred and heated at 70 °C under nitrogen atmosphere. 3-Amino-6(7)-chloro-2-quinoxalinecarbonitrile 1,4-dioxide (2.00 g, 8.46 mmol) was added. Following tert-butyl nitrite (2 mL) was injected with a needle generating an effervescence (approx. 5 min) giving a dark brown solution. Additional tert-butyl nitrite (2 mL) was necessary for completing the reaction. The mixture was stirred and heated at 70 °C for 15 min, after removal of the solvent a dark waxy solid was obtained. Flash chromatography (toluene/ethyl acetate 100/15) gave a yellow solid which was recrystallized fron ethyl acetate to give yellow crystals (28 %), mp 179 °C. IR (KBr) 3093, 2242, 1367 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 8.05 (m, 1 H, H_6); 8.47 (s, 1 H, H_8); 8.50 (m, 1 H, H_5); 8.98 (s, 1 H, H_3). MS (EI) m/e (70 eV) M^+= 221. ANAL (calc. for $C_9H_4ClN_3O_2$) C, 48.76; H, 1.81; N, 18.96. Found: C, 48.59; H, 1.78; N, 19.19.

EXAMPLE 15

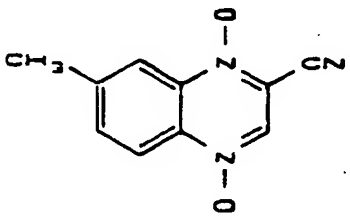
Preparation of 6,7-dichloro-2-quinoxalinecarbonitrile 1,4-dioxide



Dry N,N-DMF (45 mL) was stirred and heated at 70 °C under nitrogen atmosphere. 3-Amino-6,7-dichloro-2-quinoxalinecarbonitrile 1,4-dioxide (1.55 g, 5.72 mmol) was added. Tert-butyl nitrite (2 mL) was added. Following the addition an effervescence was observed (approx. 5 min) giving a dark brown solution. Additional tert-butyl nitrite (2 mL) was necessary to complete the reaction. The mixture was stirred and heated at 70 °C for 15 min, after removal of the solvent a dark waxy solid was obtained. Flash chromatography (toluene/ethyl acetate 100/7) gave a yellow solid which was recrystallized fron ethyl acetate to give yellow crystals (8 %), mp 206 °C. IR (KBr) 3082, 1362 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 8.67 (s, 1 H, H_5); 8.68 (s, 1 H, H_8); 9.38 (s, 1 H, H_3). MS (EI) m/e (70 eV) M^+= 255. ANAL (calc. for $C_9H_3Cl_2N_3O_2$) C, 42.19; H, 1.17; N, 16.41. Found: C, 42.66; H, 1.44; N, 16.27.

EXAMPLE 16

Preparation of 7-methyl-2-quinoxalinecarbonitrile 1,4-dioxide

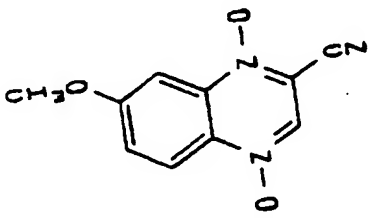


Dry N,N-DMF (35 mL) was stirred and heated at 70 °C under nitrogen atmosphere. 3-Amino-6(7)-methyl-2-quinoxalinecarbonitrile 1,4-dioxide (0.44 g, 2.04 mmol) was added. Tert-butyl nitrite (2 mL) was added. Following the addition an effervescence was observed (approx. 5 min) giving a dark brown solution. Additional

tert-butyl nitrite (2 mL) was necessary to complete the reaction. The mixture was stirred and heated at 70 °C for 15 min, after removal of the solvent a dark waxy solid was obtained. By flash chromatography (toluene/ethyl acetate 100/13) a yellow solid was obtained which was recrystallized from ethyl acetate to give yellow crystals (29 %), mp 194-195 °C. IR (KBr) 3070, 2226, 1360 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 7.90 (d, 1 H, H_6, J=8.5 Hz); 8.25 (s, 1 H, H_8); 8.34 (d, 1 H, H_5, J=8.6 Hz); 9.23 (s, 1 H, H_3). MS (EI) m/e (70 eV) M^+= 201. ANAL (calc. for $C_{10}H_7N_3O_2$) C, 59.70; H, 3.48; N, 20.89. Found: C, 60.10; H, 3.53; N, 20.58.

EXAMPLE 17

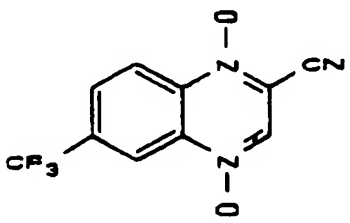
Preparation of 7-methoxy-2-quinoxalinecarbonitrile 1,4-dioxide

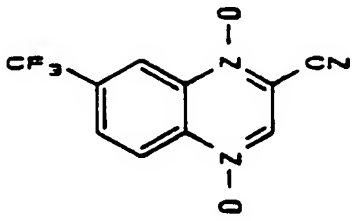


Dry N,N-DMF (50 mL) was stirred and heated at 70 °C under nitrogen atmosphere. 3-Amino-6(7)-methoxy-2-quinoxalinecarbonitrile 1,4-dioxide (1.70 g, 7.33 mmol) was added. Tert-butyl nitrite (2 mL) was added. Following the addition an effervescence was observed (approx. 5 min) giving a dark brown solution. Additional tert-butyl nitrite (2 mL) was necessary to complete the reaction. The mixture was stirred and heated at 70 °C for 15 min. After removal of the solvent a dark waxy solid was obtained. Flash chromatography (toluene/ethyl acetate 100/40) gave a yellow solid which was recrystallized fron ethyl acetate to give yellow crystals (26 %), mp 225 °C. IR (KBr) 3103, 2237, 1360 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 4.03 (s, 3 H, CH_3O); 7.61 (d, 1 H, H_6, J= 9.5 Hz); 7.74 (s, 1 H, H_8); 8.40 (d, 1 H, H_5, J= 9.6 Hz); 8.78 (s, 1 H, H_3). MS (EI) m/e (70 eV) M^+= 217. ANAL (calc. for $C_{10}H_7N_3O_3$) C, 55.30; H, 3.23; N, 19.35. Found: C, 55.52; H, 3.26; N, 19.41.

EXAMPLE 18

Preparation of 6-trifluoromethyl-2-quinoxalinecarbonitrile 1,4-dioxide and 7-trifluoromethyl-2-quinoxalinecarbonitrile 1,4-dioxide

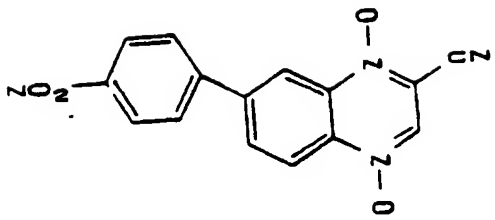




Dry N,N-DMF (50 mL) was stirred and heated at 70 °C under nitrogen atmosphere. 3-Amino-6(7)-trifluoromethyl-2-quinoxalinecarbonitrile 1,4-dioxide (1.55 g, 5.74 mmol) was added. Tert-butyl nitrite (2 mL) was added. Following the addition an effervescence was observed (approx. 5 min) giving a dark brown solution. Additional tert-butyl nitrite (2 mL) was necessary to complete the reaction. The mixture was stirred and heated at 70 °C for 15 min, after removal of the solvent a dark waxy solid was obtained. By flash chromatography (toluene/ethyl acetate 100/10) was obtained a yellow solid which was recrystallized fromn ethyl acetate to give yellow crystals (4 %) of the 6-trifluoromethyl isomer, mp 181-183 °C. IR (KBr) 3092, 2200, 1372 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 8.32 (d, 1 H, H_8, J= 8.6 Hz); 8.70 (d, 1 H, H_7, J= 9.1 Hz); 8.76 (s, 1 H, H_5); 9.08 (s, 1 H, H_3). MS (EI) m/e (70 eV) M^+= 255. ANAL (calc. for $C_{10}H_4F_3N_3O_2$) C, 48.60; H, 1.82; N, 15.90. Found: C, 48.44; H, 2.02; N, 16.26. Further elution with toluene/ethyl acetate (100/12) gave the 7-trifluoromethyl isomer, which was recrystallized from ethyl acetate (11 %), mp 161 °C. IR (KBr) 3107, 1370 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 8.33 (d, 1 H, H_5, J= 8.4 Hz); 8.71 (d, 1 H, H_6, J= 9.0 Hz); 8.73 (s, 1 H, H_8); 9.08 (s, 1 H, H_3). MS (EI) m/e (70 eV) M^+= 255. ANAL (calc. for $C_{10}H_4F_3N_3O_2$) C, 48.60; H, 1.82; N, 15.90. Found: C, 48.75; H, 2.05; N, 16.18.

EXAMPLE 19

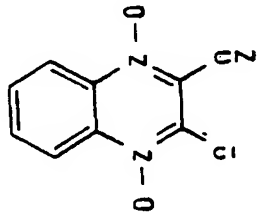
Preparation of 7-(4-nitrophenyl)-2-quinoxalinecarbonitrile 1,4-dioxide



Dry N,N-DMF (50 mL) was stirred and heated at 70 °C under nitrogen atmosphere. 3-Amino-6(7)-(4-nitrophenyl)-2-quinoxalinecarbonitrile 1,4-dioxide (1.82 g, 5.63 mmol) was added. Tert-butyl nitrite (2 mL) was added. Following the addition an effervescence was observed (approx. 5 min) giving a dark brown solution. Additional tert-butyl nitrite (2 mL) was necessary to complete the reaction. The mixture was stirred and heated at 70 °C for 15 min, after removal of the solvent a dark waxy solid was obtained. Flash chromatography (toluene/ethyl acetate 100/8) gave a yellow solid which was recrystallized fron ethyl acetate to give yellow crystals (21 %), mp 232 °C. IR (KBr) 3081, 2237, 1365 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 8.21 (d, 2 H, $H_{2'}$, $H_{6'}$, J= 8.7 Hz); 8.39 (d, 2 H, $H_{3'}$, $H_{5'}$, J= 8.7 Hz); 8.46 (d, 1 H, H_6, J= 9.2 Hz); 8.60 (d, 1 H, H_5, J= 8.9 Hz); 8.75 (s, 1 H, H_8); 9.38 (s, 1 H, H_3). MS (EI) m/e (70 eV) M^+= 308. ANAL (calc. for $C_{15}H_8N_4O_4$) C, 58.44; H, 2.60; N, 18.18. Found: C, 58.40; H, 2.64; N, 18.02.

EXAMPLE 20

Preparation of 3-chloro-2-quinoxalinecarbonitrile 1,4-dioxide

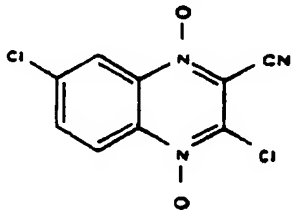


A suspension of acetonitrile (40 mL) and $CuCl_2$ (3.46 g) was stirred and heated at 70 °C under N_2 atmosphere. 3-Amino-2-quinoxalinecarbonitrile 1,4-dioxide (2.36 g,

11.68 mmol) was added. Tert-butyl nitrite (2 x 2 mL) was injected each 20 min. The mixture was heated at 70 °C for 15 min. Then was allowed to stand at room temperature. Inorganic salts were filtered off and extracted with dichloromethane (300 mL), and after removal of the solvents a brown-yellowish waxy solid was obtained. The residue was chromatographied by eluting with a gradient of toluene/ethyl acetate (100/8) giving a yellow solid. Recrystallization from ethyl acetate afforded yellow crystals (8 %), mp 197-198 °C. IR (KBr) 3102, 2237, 1344 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 7.99 (t, 2 H, H_6, H_7, J= 8.4 Hz); 8.58 (d, 1 H, H_5, J= 8.1 Hz); 8.67 (d, 1 H, H_8, J= 8.3 Hz). MS (EI) m/e (70 eV) M^+= 221. ANAL (calc. for $C_9H_4ClN_3O_2$) C, 48.76; H, 1.81; N, 18.96. Found: C, 48.98; H, 2.02; N, 18.72.

EXAMPLE 21

Preparation of 3,7-dichloro-2-quinoxalinecarbonitrile 1,4-dioxide

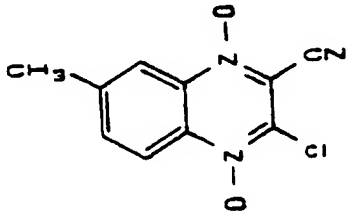


A suspension of acetonitrile (100 mL), $CuCl_2$ (6.78 g) was stirred and heated at 70 °C under N_2 atmosphere. 3-Amino-6(7)-chloro-2-quinoxalinecarbonitrile 1,4-dioxide (5.00 g, 21.14 mmol) was added. Tert-butyl nitrite (2 x 2 mL) was injected each 20 min. The mixture was heated at 70°C for 15 min and then was allowed to stand at room temperature. Inorganic salts were filtered off and extracted with dichloromethane (300 mL), and after removal of the solvents a brown-yellowish waxy solid was obtained. The residue was chromatographied by eluting with a gradient of toluene/ethyl acetate (100/13) giving a yellow solid. Finally, recrystallization from ethyl acetate afforded yellow crystals (16 %), mp 225-226 °C. IR (KBr) 3092, 2237, 1338 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 8.16 (d, 1 H, H_6, J= 9.2 Hz); 8.50 (s, 1 H, H_8);

8.52 (d, 1 H, H_5, J= 8.9 Hz). MS (EI) m/e (70 eV) M^+= 255. ANAL (calc. for $C_9H_3Cl_2N_3O_2$) C, 42.19; H, 1.17; N, 16.41. Found: C, 42.20; H, 1.12; N, 16.35.

EXAMPLE 22

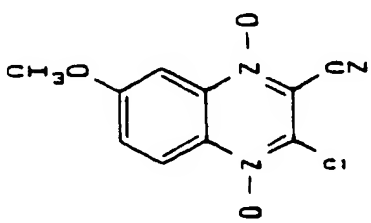
Preparation of 3-chloro-7-methyl-2-quinoxalinecarbonitrile 1,4-dioxide



A suspension of acetonitrile (100 mL), $CuCl_2$ (10.00 g) was stirred and heated at 70 °C under N_2 atmosphere. 3-Amino-6(7)-methyl-2-quinoxalinecarbonitrile 1,4-dioxide (5.50 g, 25.46 mmol) was added. Tert-butyl nitrite (2 x 2 mL every 20 min) was injected. The mixture was heated at 70°C for 15 min and was allowed to stand at room temperature. Inorganic salts were filtered off and extracted with dichloromethane (300 mL), and after removal of the solvents a brown-yellowish waxy solid was obtained. The residue was chromatographied by eluting with a gradient of toluene/ethyl acetate (100/15) giving a yellow solid. Recrystallization from ethyl acetate afforded yellow crystals (10 %), mp 210 °C. IR (KBr) 3078, 2237, 1344 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 2.51 (s, 3 H, CH_3); 7.97 (d, 1 H, H_6, J= 8.7 Hz); 8.29 (s, 1 H, H_8); 8.41 (d, 1 H, H_5, J= 8.6 Hz). MS (EI) m/e (70 eV) M^+= 235. ANAL (calc. for $C_{10}H_6ClN_3O_2$) C, 50.95; H, 2.55; N, 17.83. Found: C, 50.67; H, 2.52; N, 17.52.

EXAMPLE 23

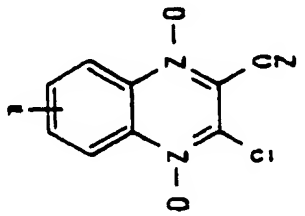
Preparation of 3-chloro-7-methoxy-2-quinoxalinecarbonitrile 1,4-dioxide



A suspension of acetonitrile (70 mL), $CuCl_2$ (8.23 g) was stirred and heated at 70 °C under N_2 atmosphere. 3-Amino-6(7)-methoxy-2-quinoxalinecarbonitrile 1,4-dioxide (3.37 g, 14.53 mmol) was added. Tert-butyl nitrite (2 x 2 mL each 20 min) was injected. The mixture was heated at 70 °C for 15 min and then was allowed to stand at room temperature. Inorganic salts were filtered off and extracted with dichloromethane (300 mL), and after removal of the solvents a brown waxy solid was obtained. The residue was chromatographied by eluting with a gradient of toluene/ethyl acetate (100/10) giving a yellow solid. Finally, recrystallization from ethyl acetate afforded yellow crystals (16 %), mp 218-220 °C. IR (KBr) 3103, 2237, 1328 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 4.03 (s, 3 H, CH_3O); 7.73 (d, 1 H, H_6, J= 7.5 Hz); 7.75 (s, 1 H, H_8); 8.43 (d, 1 H, H_5). MS (EI) m/e (70 eV) M^+= 251. ANAL (calc. for $C_{10}H_6ClN_3O_3$) C, 47.71; H, 2.39; N, 16.70. Found: C, 47.38; H, 2.38; N, 16.59.

EXAMPLE 24

Preparation of 3-chloro-6(7)-fluoro-2-quinoxalinecarbonitrile 1,4-dioxide

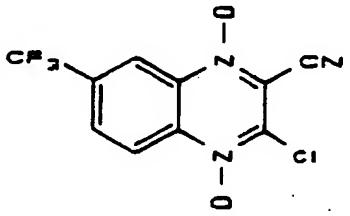


A suspension of acetonitrile (45 mL), $CuCl_2$ (4.80 g) was stirred and heated at 70 °C under N_2 atmosphere. 3-Amino-6(7)-fluoro-2-quinoxalinecarbonitrile 1,4-dioxide (3.70 g, 16.82 mmol) was added. Tert-butyl nitrite (2 x 2 mL each 20 min) was injected. The mixture was heated at 70°C for 15 min and then was allowed to stand at room temperature. Inorganic salts were filtered off and extracted with dichloromethane (300 mL), and after removal of the solvents a brown waxy solid was obtained. The residue was chromatographied by eluting with a gradient of toluene/ethyl acetate (100/6) giving a yellow solid. Recrystallization from ethyl acetate afforded yellow

crystals (21 %), mp 127-128 °C. HPLC analyses showed a mixture of 6 and 7 isomers in a ratio of 39/61. IR (KBr) 3103, 2237, 1339 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 7.84 (m, 2 H, H_6 7 isomer, H_7 6 isomer); 8.30 (s, 1 H, H_5 6 isomer); 8.34 (s, 1 H, H_8 7 isomer); 8.78 (d, 1 H, H_5 7 isomer, J= 9.4 Hz); 8.80 (d, 1 H, H_8 6 isomer, J= 9.3 Hz). MS (EI) m/e (70 eV) M^+= 239. ANAL (calc. for $C_9H_3ClFN_3O_2$) C, 45.09; H, 1.25; N, 17.54. Found: C, 45.31; H, 1.18; N, 17.59.

EXAMPLE 25

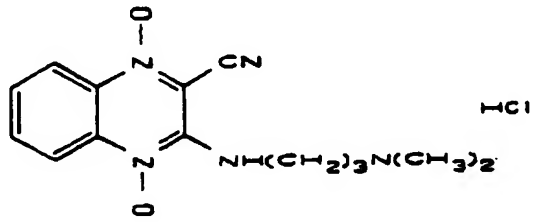
Preparation of 3-chloro-7-trifluoromethyl-2-quinoxalinecarbonitrile 1,4-dioxide



A suspension of acetonitrile (50 mL), $CuCl_2$ (6.37 g) was stirred and heated at 80 °C under N_2 atmosphere. 3-Amino-6(7)-trifluoromethyl-2-quinoxalinecarbonitrile 1,4-dioxide (5.00 g, 18.52 mmol) was added. Tert-butyl nitrite (2 x 2 mL each 20 min) was injected. The mixture was heated at 70°C for 15 min and then was allowed to stand at room temperature. Inorganic salts were filtered off and extracted with dichloromethane (300 mL), and after removal of the solvents a brown waxy solid was obtained. The residue was chromatographied by eluting with a gradient of toluene/ethyl acetate (100/2) giving a yellow solid. Recrystallization from ethyl acetate afforded yellow crystals (13 %), mp 230-232 °C. IR (KBr) 3103, 2237, 1349 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 8.41 (d, 1 H, H_6, J= 9.1 Hz); 8.71 (d, 1 H, H_5, J= 9.0 Hz); 8.80 (s, 1 H, H_8). MS (EI) m/e (70 eV) M^+= 289. ANAL (calc. for $C_{10}H_3ClF_3N_3O_2$) C, 41.45; H, 1.04; N, 14.51. Found: C, 41.39; H, 0.96; N, 14.39.

EXAMPLE 26

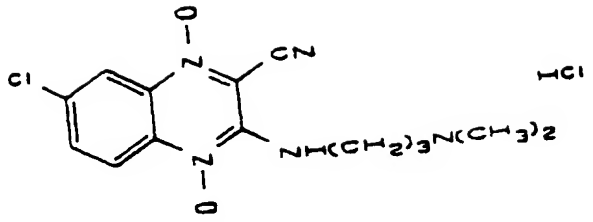
Preparation of 3-[3-(N,N-dimethylamino)propylamino]-2-quinoxalinecarbonitrile 1,4-dioxide, hydrochloride



3-Chloro-2-quinoxalinecarbonitrile 1,4-dioxide (150 mg, 0.68 mmol) was dissolved in dichloromethane (200 mL) and K_2CO_3 (94 mg, 0.68 mmol) was added. 3-(N,N-dimethylamino)-1-propylamino (71 mg, 0.70 mmol) was added dropwise. The mixture was stirred for 3 days at room temperature. Inorganic salts were filtered off and the solvent was removed by rotatory evaporation. Flash chromatography was carried out by using a gradient of ethyl acetate/methanol giving a red solid, which was dissolved in dry acetone. Addition of 3-5 drops of concentrated HCl gave a red precipitate which was recrystallized from acetone (53 %), mp 201 °C. IR (KBr) 3220, 2942, 2761, 2226, 1360 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 1.78 (q, 2 H, CH_2, J= 6.5 Hz); 2.12 (s, 6 H, 2 CH_3); 2.30 (t, 2 H, CH_2N, J= 6.3 Hz); 3.70 (c, 2 H, $NHCH_2$); 7.61 (t, 1 H, H_6, J= 7.7 Hz); 7.88 (t, 1 H, H_7, J= 7.6 Hz); 8.23 (d, 2 H, H_5, H_8, J= 8.6 Hz). MS (EI) m/e (70 eV) M^+= 287. ANAL (calc. for $C_{14}H_{17}N_5O_2 \cdot HCl$) C, 51.93; H, 5.56; N, 21.64. Found: C, 52.01; H, 5.75; N, 21.55.

EXAMPLE 27

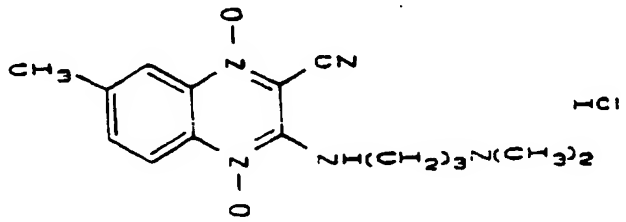
Preparation of 7-chloro-3-[3-(N,N-dimethylamino)propylamino]-2-quinoxalinecarbonitrile 1,4-dioxide, hydrochloride



3,7-Dichloro-2-quinoxalinecarbonitrile 1,4-dioxide (0.51 g, 1.99 mmol) was dissolved in dichloromethane (250 mL) and K_2CO_3 (0.27 g, 1.99 mmol) was added. 3-(N,N-dimethylamino)-1-propylamino (0.21 g, 2.06 mmol) was added dropwise. The mixture was stirred for 3 days at room temperature. Inorganic salts were filtered off and the solvent was removed by rotatory evaporation. Flash chromatography was carried out by using a gradient of ethyl acetate/methanol giving a red solid, which was dissolved in dry acetone. Addition of 3-5 drops of concentrated HCl gave a red precipitate which was recrystallized from acetone/methanol (85 %), mp 201 °C. IR (KBr) 3241, 3070, 2953, 2226, 1595, 1339, 1178, 644 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 2.21 (q, 2 H, CH_2, J= 7.5 Hz); 2.73 (s, 6 H, 2 CH_3); 3.09 (t, 2 H, CH_2N, J= 7.5 Hz); 3.77 (c, 2 H, $NHCH_2$, J= 6.5 Hz); 7.97 (d, 1 H, H_6, J= 9.2 Hz); 8.30 (d, 1 H, H_5, J= 8.9 Hz); 8.30 (s, 1 H, H_8); 8.58 (t, 1 H, NH); 10.51 (bs, 1 H, HCl). MS (EI) m/e (70 eV) M^+= 321. ANAL (calc. for $C_{14}H_{16}ClN_5O_2 \cdot HCl$) C, 46,93; H, 4,75; N, 19,55. Found: C, 47,12; H, 4,93; N, 19,38.

EXAMPLE 28

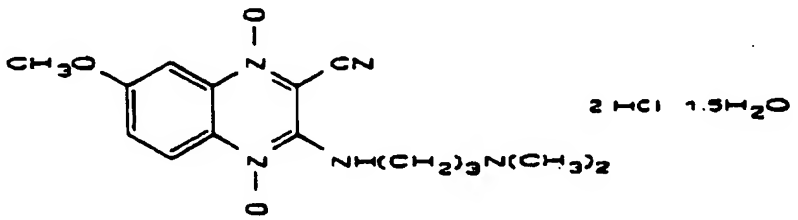
Preparation of 3-[3-(N,N-dimethylamino)propylamino]-7-methyl-2-quinoxalinecarbonitrile 1,4-dioxide, hydrochloride



3-Chloro-7-methyl-2-quinoxalinecarbonitrile 1,4-dioxide (0,23 g, 0.98 mmol) was dissolved in dichloromethane (150 mL) and K_2CO_3 (0,14 g, 1.00 mmol) was added. Afterwards 3-(N,N-dimethylamino)-1-propylamino (0,107 g, 1.05 mmol) was added dropwise. The mixture was stirred for 3 days at room temperature. Inorganic salts were filtered off and the solvent was removed by rotatory evaporation. Flash chromatography was carried out by using a gradient of ethyl acetate/methanol giving a red solid, which was dissolved in dry acetone. Addition of 3-5 drops of concentrated HCl gave a red precipitate which was recrystallized from acetone/methanol and identified as the 7 isomer (39 %), mp 203 °C. IR (KBr) 3223, 2943, 2764, 2226, 1576, 1351 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 2.12 (q, 2 H, CH_2, J= 7.1 Hz); 2.58 (s, 3 H, Ar-CH_3); 2.76 (s, 6 H, 2 CH_3); 3.12 (t, 2 H, CH_2N); 3.78 (c, 2 H, $NHCH_2$, J= 6.4 Hz); 7.81 (d, 1 H, H_6, J= 8.7 Hz); 8.12 (s, 1 H, H_8); 8.22 (d, 1 H, H_5, J= 8.8 Hz); 8.42 (t, 1 H, NH); 10.63 (bs, 1 H, HCl). MS (EI) m/e (70 eV) M^+= 284. ANAL (calc. for $C_{15}H_{19}N_5O_2 \cdot HCl$) C, 53.33; H, 5.93; N, 20.74. Found: C, 53.14; H, 6.14; N, 20.46.

EXAMPLE 29

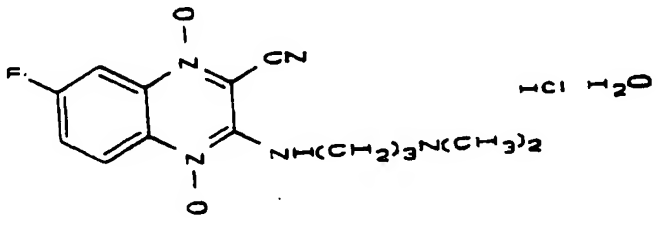
Preparation of 3-[3-(N,N-dimethylamino)propylamino]-7-methoxy-2-quinoxalinecarbonitrile 1,4-dioxide, bishydrochloride, 1.5 hydrate



3-Cloro-7-methoxy-2-quinoxalinecarbonitrile 1,4-dioxide (0,20 g, 0.80 mmol) was dissolved in dichloromethane (150 mL) and K_2CO_3 (0,11 g, 0.80 mmol) was added. 3-(N,N-dimethylamino)-1-propylamino (0,087 g, 0.85 mmol) was added dropwise. The mixture was stirred for 3 days at room temperature. Inorganic salts were filtered off and the solvent was removed by rotatory evaporation. Flash chromatography was carried out by using a gradient of ethyl acetate/methanol giving a red solid, which was dissolved in dry acetone. Addition of 3-5 drops of concentrated HCl gave a red precipitate which was recrystallized from acetone/methanol (60 %), mp 172-173 °C. IR (KBr) 3370-3306, 3028, 2942, 2718, 2226, 1600, 1376, 1275, 1237 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 2.07 (q, 2 H, CH_2); 2.69 (s, 6 H, 2 CH_3); 3.07 (t, 2 H, CH_2N); 3.74 (c, 2 H, $NHCH_2$, J= 6.2 Hz); 3.92 (s, 3 H, OCH_3); 7.56 (s, 1 H, H_8); 7.58 (d, 1 H, H_6, J= 8.0 Hz); 8.20 (d, 1 H, H_5, J= 9.9 Hz); 8.29 (t, 1 H, NH); 11.00 (bs, 1 H, HCl). MS (EI) m/e (70 eV) M^+= 317. ANAL (calc. for $C_{15}H_{19}N_5O_3 \cdot 2HCl \cdot 1.5H_2O$) C, 43.16; H, 5.76; N, 16.79. Found: C, 43.21; H, 5.86; N, 16.55.

EXAMPLE 30

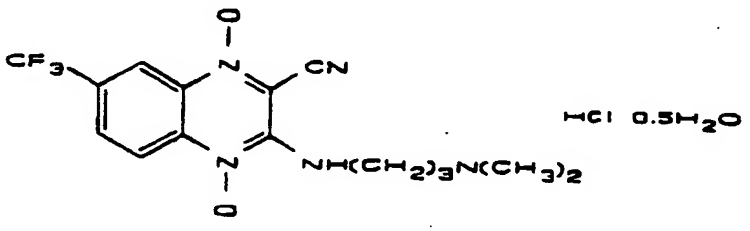
Preparation of 3-[3-(N,N-dimethylamino)propylamino]-7-fluoro-2-quinoxalinecarbonitrile 1,4-dioxide, hydrochloride, hydrate



3-cloro-6(7)-fluoro-2-quinoxalinecarbonitrile 1,4-dioxide (0,122 g, 0.51 mmol) was dissolved in dichloromethane (100 mL) and K_2CO_3 (0,071 g, 0.51 mmol) was added. 3-(N,N-dimethylamino)-1-propylamino (0,054 g, 0.53 mmol) was added dropwise. The mixture was stirred for 3 days at room temperature. Inorganic salts were filtered off and the solvent was removed by rotatory evaporation. Flash chromatography was carried out by using a gradient of ethyl acetate/methanol giving a red solid, which was dissolved in dry acetone. Addition of 3-5 drops of concentrated HCl gave a red precipitate which was recrystallized from acetone/methanol and identified as the 7 isomer (77 %), mp 170 °C. IR (KBr) 3380, 2958, 2457, 2219, 1586, 1336 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 2.01 (q, 2 H, CH_2); 2.72 (s, 6 H, 2 CH_3); 3.14 (t, 2 H, CH_2N); 3.78 (c, 2 H, $NHCH_2$); 8.08 (d, 1 H, H_6, J= 8.2 Hz); 8.23 (m, 2 H, H_5 H_8); 8.45 (t, 1 H, NH); 10.83 (bs, 1 H, HCl). MS (EI) m/e (70 eV) M^+= 305. ANAL (calc. for $C_{14}H_{16}FN_5O_2 \cdot HCl \cdot H_2O$) C, 46.73; H, 5.28; N, 19,47. Found: C, 46.48; H, 5.65; N, 19.05.

EXAMPLE 31

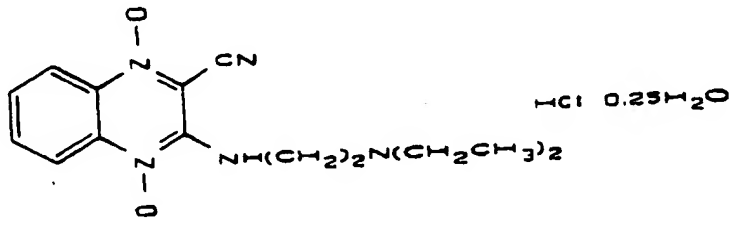
Preparation of 3-[3-(N,N-dimethylamino)propylamino]-7-trifluorometil-2-quinoxalinecarbonitrile 1,4-dioxide, hydrochloride, hemihydrate



3-cloro-(6)7-trifluorometil-2-quinoxalinecarbonitrile 1,4-dioxide (0,46 g, 1.59 mmol) was dissolved in dichloromethane (300 mL) and K_2CO_3 (0,221 g, 1.60 mmol) was added. 3-(N,N-dimethylamino)-1-propylamino (0,166 g, 1.63 mmol) was added dropwise. The mixture was stirred for 3 days at room temperature. Inorganic salts were filtered off and the solvent was removed by rotatory evaporation. Flash chromatography was carried out by using a gradient of ethyl acetate/methanol giving a red solid, which was dissolved in dry acetone. Addition of 3-5 drops of concentrated HCl gave a red precipitate which was recrystallized from acetone/methanol and identified as the 7 isomer (16 %), mp 177 °C. IR (KBr) 3412, 3188, 2953, 2451, 2226, 1563, 1339 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 2.10 (q, 2 H, CH_2, J= 7.6 Hz); 2.75 (s, 6 H, 2 CH_3); 3.10 (t, 2 H, CH_2N, J= 7.6 Hz); 3.80 (c, 2 H, $NHCH_2$, J= 6.4 Hz); 7.96 (d, 1 H, H_6, J= 8.9 Hz); 8.51 (d, 1 H, H_5, J= 10.5 Hz); 8.54 (s, 1 H, H_8); 8.73 (t, 1 H, NH); 10.18 (bs, 1 H, HCl). MS (EI) m/e (70 eV) M^+= 355. ANAL (calc. for $C_{15}H_{18}F_3N_5O_2 \cdot$ HCl $\cdot$ 0,5 H_2O) C, 44.94; H, 4.49; N, 17.48. Found: C, 45.16; H, 4.36; N, 17.02.

EXAMPLE 32

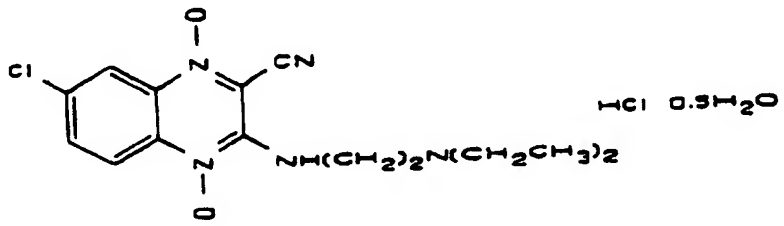
Preparation of 3-[2-(N,N-diethylamino)ethylamino]-2-quinoxalinecarbonitrile 1,4-dioxide, hydrochloride, 0.25 hydrate



A mixture of 3-chloro-2-quinoxalinecarbonitrile 1,4 dioxide (0,23 g, 1.04 mmol), K_2CO_3 (0,145 g, 1.05 mmol), 2-(N,N-diethylamino)ethylamino (0,123 g, 1.06 mmol) and CH_2Cl_2 (100 mL) was stirred at room temperature for 3 days. Inorganic salts were filtered off and, after removal of the solvent, a red solid was obtained. Flash chromatography by eluting with a gradient of AcOEt/MeOH gave a red compound, which was redissolved in acetone. The solution was treated with 3-4 drops of concentrated HCl and the red solid was filtered. Recrystallization from acetone afforded red crystals (28%), mp 176 °C. IR (KBr) 3177, 2953, 2654-2579, 2451, 2226, 1568, 1349 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 1.27 (t, 6 H, 2 CH_3, J= 7.1 Hz); 3.19 (c, 4 H, 2 NCH_2); 3.41 (t, 2 H, CH_2N); 4.12 (c, 2 H, $NHCH_2$, J= 6.2 Hz); 7.71 (t, 1 H, H_6, J= 7.7 Hz); 7.97 (t, 1 H, H_7, J= 7.7 Hz); 8.32 (d, 2 H, H_5 H_8); 8.55 (t, 1 H, NH); 10.83 (bs, 1 H, HCl). MS (EI) m/e (70 eV) M^+= 284. ANAL (calc. for $C_{15}H_{19}N_5O_2 \cdot HCl \cdot 0{,}25$ H_2O) C, 52.63; H, 5.99; N, 20.47. Found: C, 52.54; H, 6.02; N, 20.58.

EXAMPLE 33

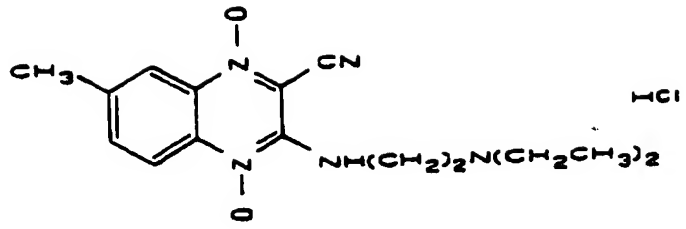
Preparation of 7-chloro-3-[2-(N,N-diethylamino)ethylamino]-2-quinoxalinecarbonitrile 1,4-dioxide, hydrochloride, hemihydrate



A mixture of 3,7-dichloro-2-quinoxalinecarbonitrile 1,4-dioxide (0,111 g, 0.43 mmol), K_2CO_3 (0,060 g, 0.43 mmol), 2-(N,N-diethylamino)ethylamino (0,055 g, 0.47 mmol) and CH_2Cl_2 (75 mL) was stirred at room temperature for 3 days. Inorganic salts were filtered off and, after removal of the solvent, a red solid was obtained. Flash chromatography by eluting with a gradient of AcOEt/MeOH gave a red compound, which was redissolved in acetone. The solution was treated with 3-4 drops of concentrated HCl and the red solid was filtered. Recrystallization from acetone afforded red crystals (70%), mp 165-166 °C. IR (KBr) 3412, 3092, 2974, 2643, 2226, 1595, 1349 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 1.25 (t, 6 H, 2 CH_3, J= 7.0 Hz); 3.19 (c, 4 H, 2 NCH_2); 3.35 (t, 2 H, CH_2N); 4.10 (c, 2 H, $NHCH_2$, J= 6.0 Hz); 7.98 (d, 1 H, H_6, J= 7.7 Hz); 8.30 (t, 1 H, H_5, J= 6.2 Hz); 8.31 (s, 1 H, H_8); 8.64 (t, 1 H, NH, J= 6.4 Hz); 10.87 (bs, 1 H, HCl). MS (EI) m/e (70 eV) M^+= 335. ANAL (calc. for $C_{15}H_{18}ClN_5O_2 \cdot HCl \cdot 0{,}5\ H_2O$) C, 47.24; H, 5.25; N, 18.37. Found: C, 47.29; H, 5.58; N, 18.04.

EXAMPLE 34

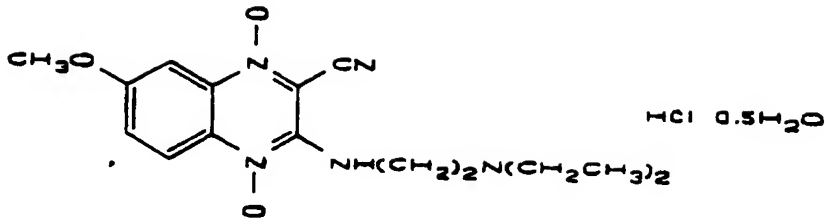
Preparation of 3-[2-(N,N-diethylamino)ethylamino]-7-methyl-2-quinoxalinecarbonitrile 1,4-dioxide, hydrochloride



A mixture of 3-chloro-7-methyl-2-quinoxalinecarbonitrile 1,4-dioxide (0,21 g, 0.89 mmol), K_2CO_3 (0,123 g, 0.89 mmol), 2-(N,N-diethylamino)ethylamino (0,107 g, 0.92 mmol) and CH_2Cl_2 (100 mL) was stirred at room temperature for 3 days. Inorganic salts were filtered off and, after removal of the solvent, a red solid was obtained. Flash chromatography by eluting with a gradient of AcOEt/MeOH gave a red compound, which was redissolved in acetone. The solution was treated with 3-4 drops of concentrated HCl and the red solid was filtered. Recrystallization from acetone afforded red crystals (37%), mp 122-123 °C. IR (KBr) 3412, 3060, 2964, 2632, 2226, 1576, 1346 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 0.99 (t, 6 H, 2 CH_3, J= 6.2 Hz); 2.47 (s, 3 H, Ar-CH_3); 2.62 (c, 4 H, 2 NCH_2); 2.81 (t, 2 H, CH_2N); 3.75 (c, 2 H, $NHCH_2$); 7.75 (d, 1 H, H_6, J= 8.7 Hz); 8.06(s, 1 H, H_8); 8.15 (t, 1 H, H_5, J= 8.8 Hz); 8.17 (t, 1 H, NH). MS (EI) m/e (70 eV) M^+= 298. ANAL (calc. for $C_{16}H_{21}N_5O_2 \cdot HCl$) C, 54.62; H, 6.26; N, 19.91. Found: C, 54.52; H, 6.02; N, 19.53.

EXAMPLE 35

Preparation of 3-[2-(N,N-diethylamino)ethylamino]-7-methoxy-2-quinoxalinecarbonitrile 1,4-dioxide, hydrochloride, hemihydrate



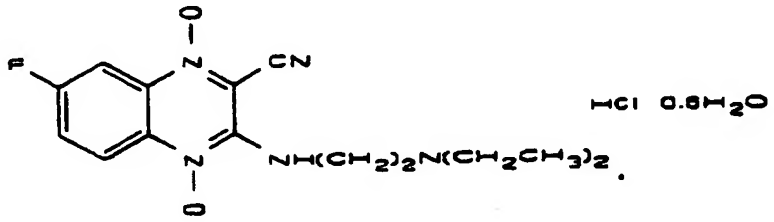
5

A mixture of 3-chloro-7-methoxy-2-quinoxalinecarbonitrile 1,4-dioxide (0,53 g, 2.11 mmol), K_2CO_3 (0,29 g, 2.12 mmol), 2-(N,N-diethylamino)ethylamino (0,25 g, 2.15 mmol) and CH_2Cl_2 (150 mL) was stirred at room temperature for 3 days. Inorganic salts were filtered off and, after removal of the solvent, a red solid was obtained. Flash chromatography by eluting with a gradient of AcOEt/MeOH gave a red compound, which was redissolved in acetone. The solution was treated with 3-4 drops of concentrated HCl and the red solid was filtered. Recrystallization from acetone afforded red crystals (14 %), mp 153 °C. IR (KBr) 3412, 3414, 2921, 2606, 2224, 1576, 1352 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 1.30 (t, 6 H, 2 CH_3, J= 7.0 Hz); 3.23 (c, 4 H, 2 NCH_2); 3.42 (t, 2 H, CH_2N); 3.99 (s, 3 H, OCH_3); 4.11 (c, 2 H, $NHCH_2$, J= 6.0 Hz); 7.63 (s, 1 H, H_8); 7.65 (d, 1 H, H_6, J= 7.8 Hz); 8.28 (d, 1 H, H_5); 8.35 (t, 1 H, NH); 10.63 (bs, 1 H, HCl). MS (EI) m/e (70 eV) M^+= 331. ANAL (calc. for $C_{16}H_{21}N_5O_3 \cdot HCl \cdot 0.5H_2O$) C, 51.00; H, 6.11; N, 18.59. Found: C, 51.24; H, 6.24; N, 18.45.

25

EXAMPLE 36

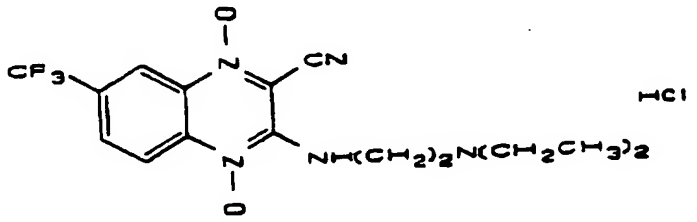
Preparation of 3-[2-(N,N-diethylamino)ethylamino]-7-fluoro-2-quinoxalinecarbonitrile 1,4-dioxide, hydrochloride, 0.6 hydrate



A mixture of 3-chloro-6(7)-fluoro-2-quinoxalinecarbonitrile 1,4-dioxide (0,18 g, 0.74 mmol), K_2CO_3 (0,105 g, 0.76 mmol), 2-(N,N-diethylamino)ethylamino (0,09 g, 0.78 mmol) and CH_2Cl_2 (100 mL) was stirred at room temperature for 3 days. Inorganic salts were filtered off and, after removal of the solvent, a red solid was obtained. Flash chromatography by eluting with a gradient of AcOEt/MeOH gave a red compound, which was redissolved in acetone. The solution was treated with 3-4 drops of concentrated HCl and the red solid was filtered. Recrystallization from acetone afforded red crystals (53 %), mp 186 °C. IR (KBr) 3412, 3423, 3092, 2964, 2643, 2226, 1579, 1349 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 1.21 (t, 6 H, 2 CH_3, J= 6.8 Hz); 3.11 (c, 4 H, 2 NCH_2); 3.50 (t, 2 H, CH_2N); 4.03 (c, 2 H, $NHCH_2$); 7.90 (d, 1 H, H_6, J= 7.6 Hz); 8.10 (m, 2 H, H_5, H_8); 8.38 (bs, 1 H, NH). MS (EI) m/e (70 eV) M^+= 319. ANAL (calc. for $C_{15}H_{18}FN_5O_2 \cdot HCl \cdot 0.6H_2O$) C, 49.14; H, 5.51; N, 19.11. Found: C, 49.01; H, 5.67; N, 18.81.

EXAMPLE 37

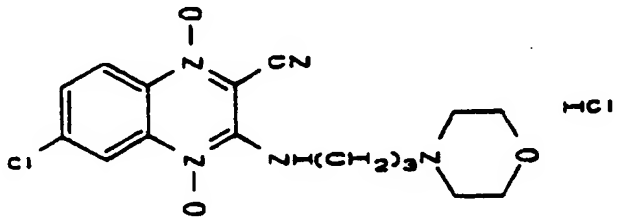
Preparation of 3-[2-(N,N-diethylamino)ethylamino]-7-trifluoromethyl-2-quinoxalinecarbonitrile 1,4-dioxide, hydrochloride

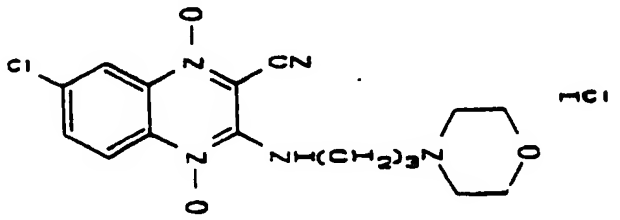


A mixture of 3-chloro-7-trifluoromethyl-2-quinoxalinecarbonitrile 1,4-dioxide (0,19 g, 0.66 mmol), K_2CO_3 (0,091 g, 0.66 mmol), 2-(N,N-diethylamino)ethylamino (0,081 g, 0.70 mmol) and CH_2Cl_2 (75 mL) was stirred at room temperature for 3 days. Inorganic salts were filtered off and, after removal of the solvent, a red solid was obtained. Flash chromatography by eluting with a gradient of AcOEt/MeOH gave a red compound, which was redissolved in acetone. The solution was treated with 3-4 drops of concentrated HCl and the red solid was filtered. Recrystallization from acetone afforded red crystals (30 %), mp 176-177 °C. IR (KBr) 3209, 3092, 2974, 2397, 2237, 1574, 1360 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 1.26 (t, 6 H, 2 CH_3, J= 6.9 Hz); 3.19 (c, 4 H, 2 NCH_2, J= 6.5 Hz); 3.37 (t, 2 H, CH_2N); 4.15 (c, 2 H, $NHCH_2$); 7.99 (d, 1 H, H_6, J= 9.0 Hz); 8.53 (d, 1 H, H_5, J= 11.0 Hz); 8.55 (s, 1 H, H_8); 8.79 (t, 1 H, NH); 10.81 (bs, 1 H, HCl). MS (EI) m/e (70 eV) M^+= 369. ANAL (calc. for $C_{16}H_{18}F_3N_5O_2$·HCl) C, 47.35; H, 4.69; N, 17.26. Found: C, 47.62; H, 4.84; N, 17.12.

EXAMPLE 38

Preparation of 6-chloro-3-[3-(4-morpholinyl)propylamino]-2-quinoxalinecarbonitrile 1,4-dioxide, hydrochloride, and 7-chloro-3-[3-(4-morpholinyl)propylamino]-2-quinoxalinecarbonitrile 1,4-dioxide, hydrochloride



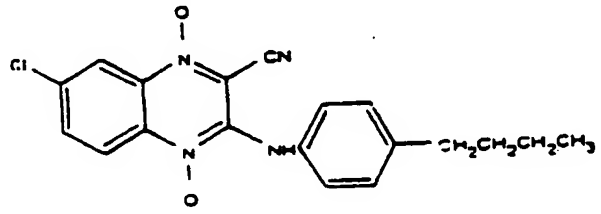


A mixture of 3,6(7)-dichloro-2-quinoxalinecarbonitrile 1,4-dioxide (0,37 g, 1.44 mmol), K_2CO_3 (0,20 g, 1.45 mmol), 4-(3-aminopropyl)morpholine (0,213 mg, 1.48 mmol) and CH_2Cl_2 (250 mL) was stirred at room temperature for 4 days. The inorganic salts were discarded and the solvent removed by evaporatory rotation. The solid residue was chromatographied with a gradient of ethyl acetate/methanol. Firstly, the isomer 6 was eluted. After removal of the solvent the red solid was redissolved in acetone and precipitated as the hydrochloride salt by addition of Hcl concentrated (2

drops). Finally it was recrystallized from acetone/methanol (6%), mp 190-191 °C. IR (KBr) 3423, 3198, 2932, 2547, 2226, 1574, 1349 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 2.16 (q, 2 H, CH_2, J= 7.2 Hz); 3.13 (t, 2 H, CH_2N); 3.32 (t, 4 H, CH_2N morpholino); 3.82 (c, 2 H, $NHCH_2$); 4.14 (t, 4 H, CH_2O morpholino); 7.70 (d, 1 H, H_7, J= 9.1 Hz); 8.29 (s, 1 H, H_5); 8.31 (d, 1 H, H_8, J= 9.4 Hz); 8.64 (t, 1 H, NH); 11.14 (bs, 1 H, HCl). MS (EI) m/e (rel. intensity, 70 eV) M^+= 346. ANAL (calc. for $C_{16}H_{18}Cl_3N_5O_3$·HCl) C, 48.00; H, 4.75; N, 17.50. Found: C, 48.04; H, 4.83; N, 17.48. The 7-chloro isomer was eluted later. After removal of the solvent the red solid was redissolved in acetone and precipitated as the hydrochloride salt, which was recrystallized from acetone/methanol (37%), mp 180-181 °C. IR (KBr) 3423, 3198, 2932, 2547, 2226, 1574, 1349 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 2.14 (m, 2 H, CH_2); 3.17 (t, 2 H, CH_2N); 3.34 (t, 4 H, CH_2N morpholino); 3.77 (c, 2 H, $NHCH_2$); 3.93 (t, 4 H, CH_2O morpholino); 7.98 (d, 1 H, H_6, J= 9.3 Hz); 8.29 (s, 1 H, H_8); 8.31 (d, 1 H, H_5, J= 9.1 Hz); 8.59 (t, 1 H, NH); 10.75 (bs, 1 H, HCl). MS (EI) m/e (70 eV) M^+= 346. ANAL (calc. for $C_{16}H_{18}Cl_3N_5O_3$·HCl) C, 48.00; H, 4.75; N, 17.50. Found: C, 47.60; H, 5.04; N, 17.82.

EXAMPLE 39

Preparation of 3-(4'-butylphenyl)amino-7-chloro-2-quinoxalinecarbonitrile 1,4-dioxide

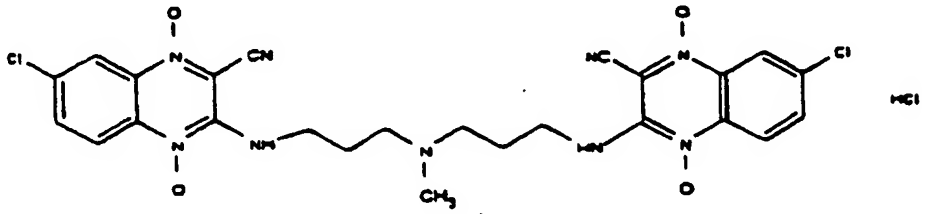


A mixture of 3,7-dichloro-2-quinoxalinecarbonitrile 1,4-dioxide (0.13 g, 0.51 mmol) and excess 4-butylaniline was stirred at room temperature for 24 h. The red solid was filtered and washed with a mixture of petroleum ether/ethyl acetate (9/1) (16 %), mp 207 °C. IR (KBr) 3165, 2929, 2227, 1593, 1361 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 0,90 (t, 3 H, CH_3, J= 7,0 Hz); 1,32 (m, 2 H, CH_2); 1,57 (m, 2 H, CH_2); 2,60 (t, 2 H, CH_2, J= 7,0 Hz); 7,24 (m, 4 H, H_2, H_3, H_5, H_6); 8,01 (d, 1 H, H_5, J=

9,1 Hz); 8,33 (s, 1 H, H_8); 8,38 (d, 2 H, H_6); 10,12 (bs, 1 H, NH). MS (EI) m/e (70 eV) M^+= 364.5. ANAL (calc. for $C_{19}H_{17}ClN_4O_2$) C, 61,80; H, 4,61; N, 15,19. Found: C,61,80; H, 4,86; N,14,90.

EXAMPLE 40

Preparation of N-methyl-N,N-bis-[N'-(7-chloro-2-cyanoquinoxalinyl 1,4-dioxide)aminopropyl]amine, hydrochloride

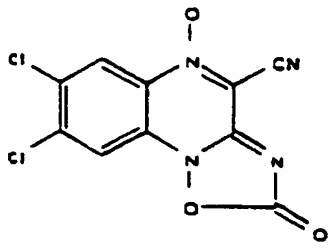


3,7-Dichloro-2-quinoxalinecarbonitrile 1,4-dioxide (0.35 g, 1.37 mmol) was dissolved in dichloromethane (150 mL). K_2CO_3 (0.19 g) and N,N-[di-(3-aminopropyl)]methylamine (0.10 g, 0.69 mmol) were added giving a red solid in suspension. The mixture was stirred at room temperature for 4 days. After filtering the insoluble salts and removal of the solvent by rotatory evaporation, a red solid was obtained. Flash chromatography by eluting with a gradient of ethyl acetate/methanol afforded a red solid which was recrystallized from methanol (25 %), mp 195 °C. IR

(KBr) 3370, 3070, 2953, 2226, 1574, 1339, 1178 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 2,12 (m, 4 H, 2 CH_2); 2,77 (m, 4 H, 2 CH_2N); 3,15-3,20 (bs, 3 H, NCH_3); 3,79 (m, 4 H, 2 NCH_2); 7,98 (d, 2 H, 2 H_5, J= 9,8 Hz); 8,32 (m, 4 H, 2 H_6 2 H_8); 8,61 (t, 2 H, 2 NH); 10,01 (bs, 1 H, HCl). ANAL (calc. for $C_{25}H_{23}Cl_2N_9O_4 \cdot HCl$) C, 48,35; H, 3,88; N, 20,31. Found: C, 48,19; H, 4,01; N, 20.00.

EXAMPLE 41

Preparation of 7,8-dichloro-4-cyano-2-oxo-1,2,4-oxadiazolo[2,3-a]quinoxaline 5-oxide

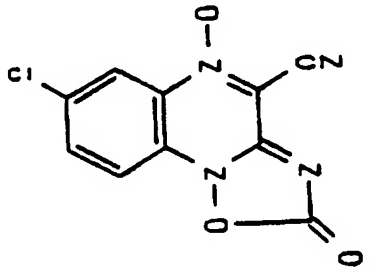


An homogeneous mixture of dry 3-amino-6.7-dichloro-2-quinoxalinecarbonitrile 1,4-dioxide (1.00 g, 3.70 mmol), dry dioxane (20 mL) and 2-chloroethyl isocyanate (2.40 g, 22.75 mmol) was stirred and heated at 100-110 °C for 24 h. Toluene (20 mL) was added and the mixture was filtrated through active charcoal-celite. The yellow solution was allowed to stand overnight at room temperature. The yellow crystals were filtrated and washed with toluene and diethyl ether (22 %), mp 268 °C. IR (KBr) 2232,

1805, 1550, 1400, 750. ^{1}H NMR (dimethylsulfoxide-d_6) 8,68 (s, 1 H, H_6); 8,78(s, 1 H, H_9). MS (EI) m/e (70 eV) M^+=296. ANAL (calc. for $C_{10}H_2Cl_2N_4O_3$) C, 40,40; H, 0,68; N, 18,85; Found: C, 40,24; H, 0,68; N, 18,82.

EXAMPLE 42

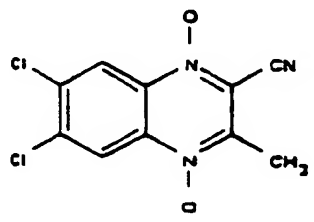
Preparation of 7-chloro-4-cyano-2-oxo-1,2,4-oxadiazolo[2,3-a]quinoxaline 5-oxide



An homogeneous mixture of dry 3-amino-7-chloro-2-quinoxalinecarbonitrile 1,4-dioxide (1.50 g, 6.30 mmol), 2-chloroethyl isocyanate (4.08 g, 38.73 mmol) and dry dioxane (20 mL) was stirred and heated at 100 °C-100°C for 24 h. Toluene (20 mL) was added and the mixture was filtrated through active charcoal/celite. Then it was allowed to stand overnight. The yellow crystals were filtrated and washed with toluene and ethylic ether. Finally was recrystallized from toluene (60%), mp 186 °C. IR (KBr): 2234, 1814, 1544, 1395 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6) 8.15 (d, 1 H, H_9); 8.24 (d, 1 H, H_{10}); 8.54 (s, 1 H, H_7). MS (EI) m/e (70 eV) M^+= 262. ANAL (calc. for $C_{10}H_3ClN_4O_2$) C, 45.71; H, 1.14; N, 21.33. Found: C, 46.46; H, 1.32; N, 21.41.

EXAMPLE 43

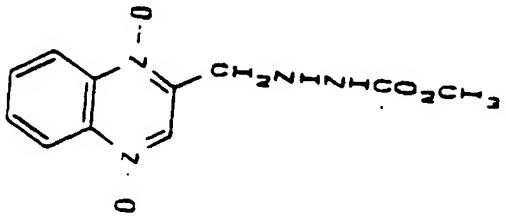
Preparation of 6,7-dichloro-3-methyl-2-quinoxalinecarbonitrile 1,4-dioxide



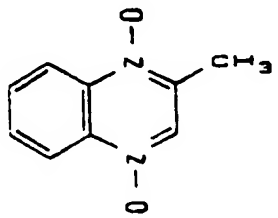
NH_3 was bubbled for 5 min through a suspension of 5,6-dichlorobenzofuroxane (1.16 g, 5.65 mmol) in methanol (1,5 mL). A mixture of 5-methylisoxazole (0.41 g, 4.93 mmol) in methanol (0.5 mL) and a solution of KOH (0.27 g, 4.81 mmol) in methanol (2.5 mL) was added and the resulting mixture was stirred for 12 h. The yellow solid obtained was filtered off and recrystallized from chloroform/methanol (36 %), mp 204-205 °C. IR (KBr) 3090, 1380 cm^{-1}. ^1H NMR (dimethylsulfoxide-d_6) 2,62 (s, 3 H, CH_3), 8,69 (s, 2 H, H_5 H_8). MS (EI) m/e (70 eV) M^+= 269. ANAL (calc. for $C_{10}H_5Cl_2N_3O_2$) C,44,44; H,1,85; N,15,56. Found: C,44,69; H,1,95; N,16,11.

EXAMPLE 44

Preparation of 2-(methoxycarbonylhydrazino)methylquinoxaline 1,4-dioxide



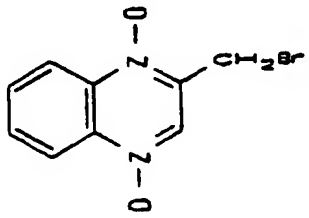
A) Preparation of 2-methylquinoxaline 1,4-dioxide



A dissolution of benzofuroxane (27.20 g, 0.20 mol) in dry acetone (50 mL) was

saturated with NH_3. The mixture was heated under reflux for 5 h. After cooling a yellow precipitate was obtained and recrystallized fron ethanol as yellow needles (71%), mp 171-172 °C.IR (KBr) 1600, 1330, 1280 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6) 2,61 (s,3H,CH_3); 7,60-7,91 (m, 2H, H_6, H_7); 8,20-8,60 (m, 2H, H_5, H_8). ANAL (calc. for $C_9H_8N_2O_2$) C, 61,36; H, 4,58; N, 15,90. Found: C, 61,49; H, 4,60; N, 15,93.

B) Preparation of 2-bromomethylquinoxaline 1,4-dioxide

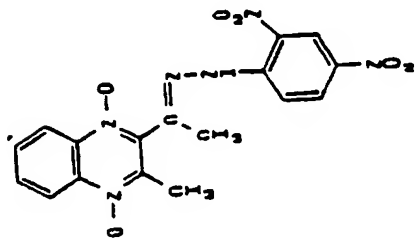


A dissolution of 2-methylquinoxaline 1,4-dioxide (0.01 mol) in glacial acetic acid (50 mL) was stirred at 12 °C. A solution of bromine (15.00 mmol) in glacial acetic acid (20 mL) was added dropwise over the first dissolution. After stirring at 12-20 °C for 12 h, ethanol (40 mL) and aqueous $NaHCO_3$ solution (100 mL) were added. The yellow precipitate was filtered and recrystallized from ethanol (56%), mp 162-164 °C. This compound was used without further purification.

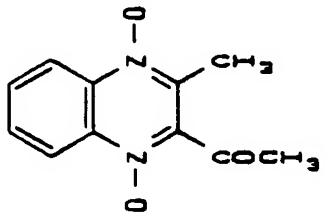
C) A solution of 2-bromomethylquinoxaline 1,4-dioxide (1.00 g, 4.40 mmoL) in ethanol was stirred at room temperature and mixed with another solution of methylcarbazate (1 g.; 11 mmoL) in ethanol (20 mL). The resulting mixture was heated under reflux for 8 h. After removal of the solvent a black oil was obtained and treated with cold methanol (5 mL) giving a yellow solid, which was recrystallized from methanol as yellow cristals (61%), mp 177-181 °C. IR (KBr) 3370-3250, 1720, 1345, 1290 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6) 3,65 (s, 3H, CH_3); 4,05 (s, 2H, CH_2); 7,38-7,56 (m, 2H, H_6, H_7); 8,01-8,22 (m, 2H, H_5, H_8); 8,53 (s, 1H, H_3). ANAL ($C_{11}H_{12}N_4O_4$) C, H, N.

EXAMPLE 45

Preparation of 2-[1-[(2,4-dinitrophenylamino)imino]ethyl]-3-methylquinoxaline 1,4-dioxide :



A) Preparation of 2-acetyl-3-methylquinoxaline 1,4-dioxide



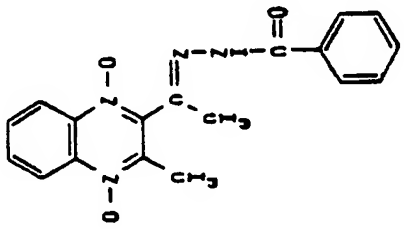
Acetylacetone (12.00 g, 0.12 mol) was dropwise added over a cooled (0 °C) solution of benzofuroxane (13.60 g, 0.10 mol) in morpholine (120 mL). The mixture was stirred at room temperature for 12 h. The yellow precipitate was collected and washed with cold isopropanol. Finally, recrystallization from isopropanol afforded yellow crystals (89%), mp 151-153 °C. IR (KBr) 1700, 1330, 1275 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6) 2,48 (s, 3H, CH_3); 2,70 (s, 3H, CH_3); 7,78-8,02 (m, 2H, H_6, H_7); 8,31-8,63 (m, 2H, H_5, H_8). ANAL (calc. for $C_{11}H_{10}N_2O_3$) C, 60,55; H, 4,62; N, 12,84. Found: C, 60,65; H, 4,51; N, 12,91.

B) A mixture of 2,4-dinitrophenylhydrazine (2.18 g, 15 mmol), ethanol (50 mL), water (10 mL) and concentrated sulphuric acid (15 mL) was dropwise added over a solution of 2-acetyl-3-methylquinoxaline 1,4-dioxide (2.10 g, 10.00 mmol). The resulting mixture was stirred and heated under reflux for 2 h. After cooling an orange solid was obtained, filtrated and recrystallized from ethanol/N,N-DMF (40%), mp 221-223 °C. IR (KBr): 3298, 1616, 1326, 1277 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6) 2,47

(s,3H, CH_3); 2,56 (s, 3H, CH_3-C=N); 7,87-8,01 (m, 3H, H_6', H_6, H_7); 8,41-8,55 (m, 3H, H_5', H_5, H_8); 8,91 (s, 1H, H_3'); 11,15 (s, 1H, NH). ANAL (calc. for $C_{17}H_{14}N_4O_6$) C, 51,25; H, 3,51; N, 21,10. Found: C, 51,46; H, 3,51; N, 21,39.

EXAMPLE 46

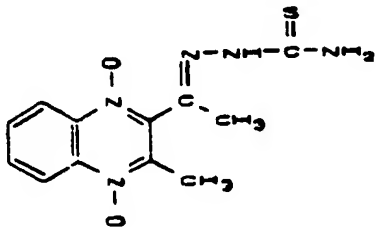
Preparation of 2-[1-(benzoylamino)imino]ethyl-3-methylquinoxaline 1,4-dioxide



A mixture of 2-acetyl-3-methylquinoxaline 1,4-dioxide (1.00 g, 4.58 mmol), benzylhydrazine (2.40 g, 9.16 mmol), sulfuric acid (2 drops) and ethanol (20 mL) was stirred and refluxed for 3 h. On cooling, the solid was collected and washed with cold ethanol. Recrystallization from ethanol afforded a yellow powder (52%), mp 202-204 °C. IR(KBr): 3170, 1692, 1332, 1274 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6): 2,38 (s, 3H, CH_3); 2,51 (s,3H, CH_3-C=N); 7,53-7,56 (m, 3H, H_3', H_4', H_5'); 7,91-7,99 (m, 4H, H_2', H_6', H_6, H_7); 8,51 (m, 2H, H_5, H_8); 11,17 (s, 1H, NH). ANAL (calc. for $C_{18}H_{16}N_4O_3$) C, 64,28; H, 4,76; N, 16,66. Found: C, 64,46; H, 4,98; N, 16,78.

EXAMPLE 47

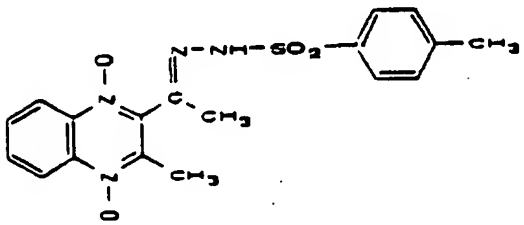
Preparation of 2-[1-(aminotiocarbonylamino)imino]ethyl-3-methylquinoxaline 1,4-dioxide



A mixture of 2-acetyl-3-methylquinoxaline 1,4-dioxide (1.00 g, 4,58 mmol), thiosemicarbazide, ethanol(20 mL) and concentrated HCl (2 drops) was stirred and refluxed for 20 h. After cooling a precipitate was obtained, filtered and recrystallized from ethanol/N,N-DMF (60%), mp 233-235 °C. IR (KBr): 3366, 1331, 1280 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6) 2,07 (s,3H, CH_3); 2,29 (s, 3H, CH_3-C=N); 7,93-7,97 (m, 3H, H_6', NH_2); 8,38-8,51 (m, 3H, H_5, H_7, H_8); 10,76 (s, 1H, NH). ANAL (calc. for $C_{12}H_{13}N_5O_2S$) C, 49,48; H, 4,46; N, 24,05. Found: C, 49,76; H, 4,49; N, 23,89.

EXAMPLE 48

Preparation of 1-[(4-methylphenylsulfonylamino)imino]ethyl-3-methylquinoxaline 1,4-dioxide

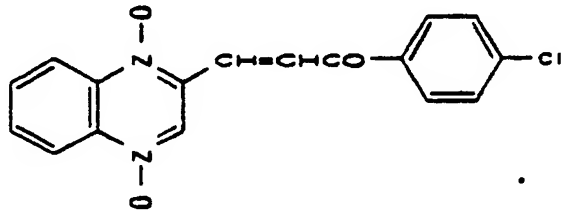


A mixture of p-toluensulfonylhydrazine (1.70 g, 9.17 mmol), ethanol (10 mL) and concentrated sulphuric acid (2 drops) was dropwise added over a mixture of 2-acetyl-3-methylquinoxaline 1,4-dioxide (1.00 g, 4,58 mmol) and ethanol (10 mL). The complete mixture was stirred and heated for 12 h. After removal of the solvent, an oil was obtained, treated with isopropanol and recrystallized from ethanol/N,N-DMF

(65%), mp 218-223 °C. IR (KBr): 2990, 1420, 1334, 1287 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6) 2,01 (s,3H, CH_3-Ar); 2,17 (s, 3H, CH_3); 2,39 (s, 3H, CH_3-C=N); 7,39-7,43 (d, 2H, H_3', H_5'); 7,74-7,78 (d, 2H, H_2', H_6'); 7,86-7,97 (m, 2H, H_6, H_7); 8,37-8,45 (m, 2H, H_5, H_8), 11,21 (s, 1H,NH). ANAL (calc. for $C_{18}H_{18}N_4O_4S$) C, 55,90; H, 4,66; N, 14,50. Found: C, 56,23; H, 4,88; N, 14,58.

EXAMPLE 49

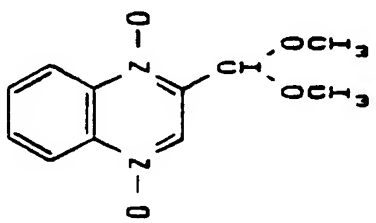
Preparation of 2-[3-(p-chlorophenyl)-3-oxo-1-propenyl]quinoxaline 1,4-dioxide



A) Preparation of p-chorobenzoylmethylentriphenylphosphorane.

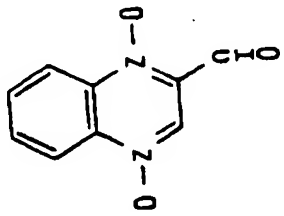
To a solution of p-chlorophenylbromomethylketone (0.10 mol) in anhidrous benzene (100 mL) was added a solution of triphenylphosphine (0.10 mol) in anhidrous benzene (100mL). The mixture was stirred at room temperature for 30 min. The white phosphonium salt was filtrated and dissolved in methanol (200 mL). Sodium methoxide (0.10 mol) in 200 mL of water was added. After stirring for 2 h., additional 400 mL of water were added. The organic compound was extracted with diethyl ether (4 x 120 mL) and dried over dry Na_2SO_4. After removal of the solvent, the yellow residue crystallized from a mixture of benzene/petroleum ether. The phosphorane was used without further purification.

B) Preparation of 2-dimethoxymethylquinoxaline 1,4-dioxide



Pyruvaldehyde dimethylacetal (11.80 g, 0,10 mol) was dropwise added over a cooled (0 °C) solution of benzofuroxane (13.60 g, 0,10 mol) in diethyl ether (60 mL). Pyrrolidine (2 drops) was added. The colour of the solution changed from yellow to purple. After stirring for 12 h. at room temperature, a yellow precipitate was isolated. Recrystallization from ethanol afforded yellow crystals (78%), mp 145-146 °C. IR (KBr): 1610, 1335, 1280 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6): 3,6 (s, 6H, CH_3); 5,9 (s, 1H, CH); 7,65-7,95 (m, 2H, H_6, H_7); 8,37-8,70 (m, 2H, H_5, H_8); 8,43 (s, 1H, H_2). ANAL (calc. for $C_{11}H_{12}N_2O_4$) C, 55,93; H, 5,12; N, 11,86. Found: C, 55,73; H, 5,01; N, 11,93.

C) Preparation of 2-formylquinoxaline 1,4-dioxide



Concentrated HCl (4 mL) was added dropwise over a dissolution of 2-dimethoxymethylquinoxaline 1,4-dioxide (2.36 g, 0,01 mol) in ethanol (30 mL). The mixture was heated in a water bath for 60 min. The mixture was stirred at room temperature for 24 h. After removed of the solvent, a residue was obtained and recrystallized from chloroform (67%), mp 208-212 °C. IR (KBr): 1685, 1340, 1275 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6): 7,81-8,15 (m, 2H, H_6, H_7); 8,24-8,60 (m, 2H, H_5, H_8); 8,46 (s, 1H, H_2); 10,25 (s, 1H, CHO).

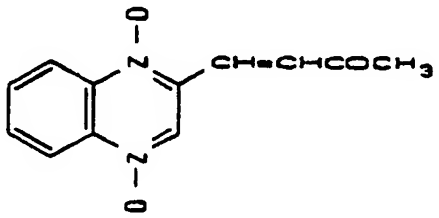
This compound was used without further purification.

D) 2-Formylquinoxaline 1,4-dioxide (0.10 mol) and p-chlorobenzoylmethylentriphenylphosphorane (0.10 mol) were dissolved in chloroform (25 mL). The mixture was heated under reflux for 6 h. After removal of the solvent, the residue was recrystallized from ethanol (59%), mp 205-208 °C. IR (KBr): 1600, 1330,

1280 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6): 7,68 (d, 2H, H_3', H_5');8,33 (d, 1H, CH); 8,38 (d, 2H, H_2', H_6'); 8,20-8,80 (m, 2H, H_6, H_7); 8,80-9,09 (m, 2H, H_5, H_8); 8,82 (d, 1H, CH); 9,88 (s, 1H, H_3). ANAL ($C_{17}H_{11}ClN_2O_3$) C, H, N.

EXAMPLE 50

Preparation of 2-(3-oxo-1-butenyl)quinoxaline 1,4-dioxide



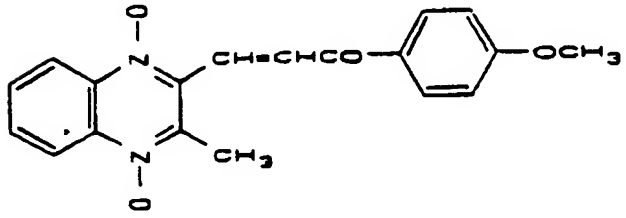
A) Preparation of acetylmethylentriphenylphosphorane.

To a solution of bromoacetone (0.10 mol) in anhidrous benzene (100 mL) was added a solution of triphenylphosphine (0.10 mol) in anhidrous benzene (100 mL). The mixture was stirred for 30 min. The white solid was filtered and dissolved in methanol (200 mL). Sodium methoxide (0.10 mol) in 200 mL of water was added. The mixture was stirred for 2 h. Water (400 mL) was added, and the organic compound extracted with diethyl ether (4 x 120 mL). The organic layer was dried over Na_2SO_4. After removal of the solvent, the crude solid was recrystallized from benzene/petroleum ether. The phosphorane was used without further purification.

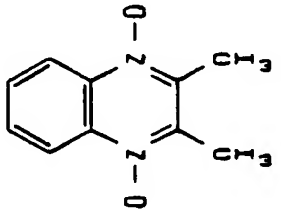
B) 2-formylquinoxaline 1,4-dioxide (0.10 mol) and acetylmethylentriphenylphosphorane (0.10 mol) were dissolved in chloroform (25 mL). The mixture was heated under reflux for 6 h. After removal of the solvent, the residue was recrystallized from ethanol (65%), mp 197-199 °C. IR (KBr): 1600, 1320, 1265 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6): 2,53 (s, 3H, CH_3); 7,73 (d, 1H, CH); 8,33 (d, 1H, CH); 8,36 (m, 2H, H_6, H_7); 8,91 (m, 2H, H_5, H_8); 9,56 (s, 1H, H_3). ANAL ($C_{12}H_{10}N_2O_3$) C, H, N.

EXAMPLE 51

Preparation of 2-[3-(4-methoxyphenyl)-3-oxo-1-propenyl]-3-methylquinoxaline 1,4-dioxide

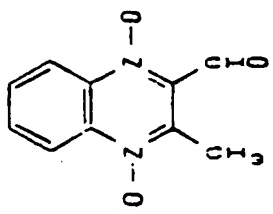


A) Preparation of 2,3-dimethylquinoxaline 1,4- dioxide



A cooled (5 °C) solution of benzofuroxane (13.60 g, 0.10 mol) and morpholine (120 mL) was stirred for 10 min. Butanone (9.60 g, 0.12 mol) was added dropwise. The mixture was stirred at room temperature for 24 h. Reaction was carried on by TLC. After removal of the solvent, a brown gum was obtained and triturated with methanol (50 mL). The solid was recrystallized from ethanol as yellow crystals (63%), mp 192-193 °C. IR(KBr): 1605, 1320, 1280 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6): 2,70 (s, 6H, CH_3); 7,60-7,84 (m, 2 H, H_6, H_7); 8,30-8,60 (m, 2H, H_5, H_8). ANAL (calc. for $C_{10}H_{10}N_2O_2$) C, 63,15; H, 5,30; N, 14,73. Found: C, 63,31; H, 5,42; N, 14,53.

B) Preparation of 2-formyl-3-methylquinoxaline 1,4-dioxide



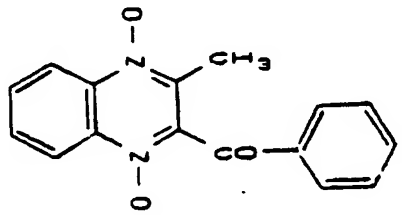
2,3-Dimethylquinoxaline 1,4-dioxide (3.80 g, 0.02 mol) was dissolved in hot ethyl acetate (150 mL). Selenium dioxide (2.30 g, 0.02 mol) was added. The mixture was heated under reflux for 4 h. After removal of the solvent a dark-red residue was obtained and extracted with hot chloroform. The solvent was removed and a yellow solid was obtained. Recrystallization from ethanol yielded yellow crystals (73%), mp 181-184 °C.

This compound was used without further purification.

C) A mixture of 2-formyl-3-methylquinoxaline 1,4-dioxide (1.90 g, 0.01 mol) and p-methoxybenzoylmethylentriphenylphosphorane (0.01 mol) and chloroform (50 mL) was heated under reflux for 12 h. After removal of the solvent a brown residue was obtained. Recrystallization from ethanol/N,N-DMF gave yellow crystals (60%), mp 197-198 °C. IR (KBr): 1660, 1610, 1340, 1280 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6): 2,97 (s, 3H, CH_3); 3.95 (s, 3 H, OCH_3); 7.12 (d, 2 H, H_3, H_5); 7.85-8.10 (m, 2 H, H_6 H_7); 7.95 (d, 1 H, CH); 8.28 (d, 2 H, H_2, H_6); 8.65-8.95 (m, 2 H, H_5 H_8); 9.38 (d, 1 H, CH). ANAL (calc. for $C_{19}H_{16}N_2O_4$) C, 67.85; H, 4.79; N, 8.33. Found: C, 67.66; H, 4.90; N, 8.17.

EXAMPLE 52

Preparation of 2-benzoyl-3-methylquinoxaline 1,4-dioxide

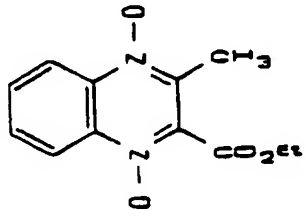


A solution of benzoylacetone (19.40 g, 0.12 mol) in morpholine (20 mL) was dropwise added over a cooled (0 °C) solution of benzofuroxane (13.60 g, 0.1 mol) in morpholine (100 mL). The mixture was stirred at room temperature for 5 h. The yellow precipitate was collected by filtration and recrystallized fron ethanol as yellow plates

(87%), mp 224-225 °C. IR (KBr) 1680, 1335, 1285 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6) 2,55 (s,3H, CH_3); 7,47-8,17 (m, 7H, H_6, H_7, 5H Ar); 8,51-8,89 (m, 2H, H_5, H_8). ANAL (calc. for $C_{16}H_{12}N_2O_3$) C, 68,56; H,4,31; N, 9,99.Found: C, 68,77; H, 4,40; N, 10,07.

EXAMPLE 53

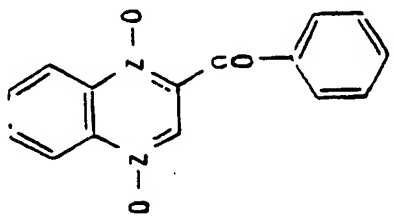
Preparation of 2-ethoxycarbonyl-3-methylquinoxaline 1,4-dioxide



A mixture of benzofuroxane (13.60 g, 0.10 mol) and ethyl acetylacetate (13.00 g, 0.10 mol) was stirred at 0 °C. Morpholine was dropwise added (17.40 g, 0.20 mol). After stirring at 0 °C for 6 h., the mixture was cooled at -25 °C and stirred for 12 h. The brown precipitate was collected and recrystallized fron ethanol as a yellow solid (82%), mp 133-134 °C. IR (KBr) 1740, 1335, 1290 cm^{-1}. ^{1}H-NMR: 1,36 (t, 3H, CH_3; 2,50 (s, 3H, CH_3); 4,55 (c, 2H, CH_2); 7.81-8.10 (m, 2H, H_6, H_7); 8,19-8,55 (m, 2H, H_5, H_8). ANAL (calc. for $C_{12}H_{12}N_2O_4$) C, 58.06; H, 4,87; N, 11,28. Found: C, 58,23; H, 4,55; N, 11,20.

EXAMPLE 54

Preparation of 2-benzoylquinoxaline 1,4-dioxide



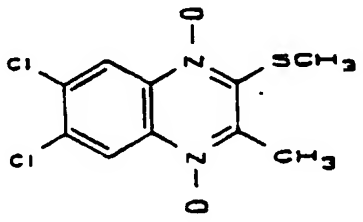
A) Preparation of ethylbenzoylpyruvate.

Potassium (27 g, 0.67 mol) was added carefully over dry diethyl ether (200 mL) under nitrogen. Ethanol (6 x 30 mL) was added. The final solution was diluted with diethyl ether (1500 mL) and diethyl oxalate (98 g, 0,67 mol) was added. After stirring for 15 min, acetophenone (92 g, 0.70 mol) was introduced and a yellow dissolution was obtained and precipitated a yellow solid. The filtered solid washed with ethyl ether. The potassium salt was mixed with concentrated sulfuric acid (60 mL) and dry ethyl ether (750 mL) in a cooled (0 °C) system. The complete mixture was stirred for 2 h. The organic solution was washed with aqueous sodium bicarbonate and then with water. The organic layer was dried over sodium sulfate. After removal of the solvent a yellow-reddish oil was obtained which crystallized on cooling (65%).

B) A solution of ethylbenzoylpyruvate (16.40 g, 0.12 mol) in triethylamine (50 mL) and ethylacetate (30 mL) was slowly added over another solution of benzofuroxane (13.60 g, 0,10 mol) in triethylamine (200 mL). The resulting mixture was stirred at room temperature for 72 h. Reaction was carried on by TLC. The yellow solid was collected and recrystallized from ethanol-DMF as yellow cristals (63%), mp 240-243 °C. IR(KBr): 1695, 1375, 1225 cm^{-1}. ^{1}H-NMR (chlorophorm-d): 7,45-7,75 (m, 3H, H_3', H_4', H_5'); 7,80-8,11 (m, 4H, H_2', H_6', H_6, H_7), 8,35 (s, 1H, H_3); 8,50-8,82 (m, 2H, H_5, H_8). ANAL (Calc. for $C_{15}H_{10}N_2O_3$) C, 67,77; H, 3,78; N, 10,52. Found: C, 67,87; H, 3,92; N, 10,18.

EXAMPLE 55

Preparation of 6,7-dichloro-3-methyl-2-methylthioquinoxaline 1,4-dioxide



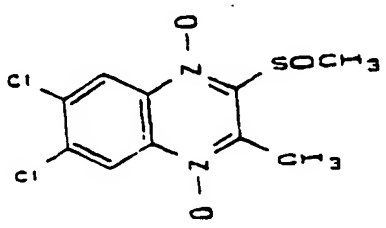
A) Preparation of 1-methylthiopropanone

1-Chloropropanone (2.90 g, 31.30 mmol) was added to a solution of sodium thiomethoxide (2.20 g, 31.40 mmol) in ethanol at 0 °C. The resulting mixture was stirred and heated under reflux for 2 h. After cooling, the inorganic salts were filtered off and the solvent was removed giving a brown gum (90%). This compound was used without further purification.

B) A solution of 1-methylthiopropanone (1.10 g, 10.50 mmol) and 5,6-dichlorobenzofuroxane (2.30 g, 11.20 mmol) in methanol (10 mL) was bubbled with dry ammonia for 10 min. The mixture was allowed to stand at room temperature overnight. The precipitated solid was filtered and recrystallized from methanol-chloroform (30%), mp 184-185 °C. IR (KBr): 1594, 1374 cm^{-1}. ^1H-NMR (d-chloroform) 2,65 (s, 3H, CH_3); 2.82 (s, 3 H, SCH_3); 8.62 (s, 1 H, H_5); 8.66 (s, 1 H, H_8). MS (EI) m/e (70 eV) M^+= 290. ANAL (calc. for $C_{10}H_8Cl_2N_2O_2S$) C, 41.24; H, 2.75; N, 9.62. Found: C, 41.09; H, 2.77; N, 9.56.

EXAMPLE 56

Preparation of 6,7-dichloro-2-methyl-3-methylsulfinylquinoxaline 1,4-dioxide

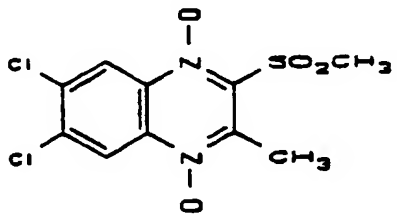


A solution of 6,7-dichloro-2-methyl-3-methylthioquinoxaline 1,4-dioxide (1.50 g, 5.10 mmol) in chloroform (10 mL) was stirred at 0 °C for 10 min. 3-Chloroperbenzoic

acid (1.00 g, 5.80 mmol) dissolved in chloroform (15 mL) was added. The mixture was stirred at room temperature for 12 h. The solution was washed with aqueous sodium bicarbonate. After drying the organic layer over sodium sulfate the solvent was removed. The resulting solid was recrystallized from methanol-chloroform (70%), mp 202-203 °C. IR (KBr): 1370, 1028 cm^{-1}. ^{1}H-NMR (d-chloroform) 2,90 (s, 3H, CH_3); 3.24 (s, 3 H, $SOCH_3$); 8.46 (s, 1 H, H_8); 8.63 (s, 1 H, H_5). MS (EI) m/e (70 eV) M^+= 306. ANAL (calc. for $C_{10}H_6Cl_2N_2O_3S$) C, 39.09; H, 2.61; N, 9.12. Found: C, 39.11; H, 2.70; N, 8.92.

EXAMPLE 57

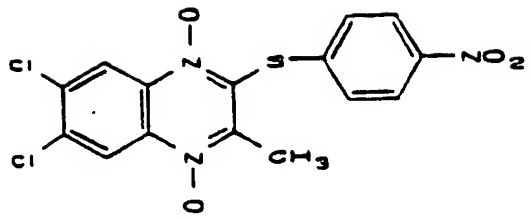
Preparation of 6,7-dichloro-2-methyl-3-methylsulfonylquinoxaline 1,4-dioxide



A solution of 3-chloroperbenzoic acid (1.86 g, 10.80 mmol) in chloroform (18 mL) was slowly added over a cooled (0 °C) solution of 6,7-dichloro-2-methyl-3-methylthioquinoxaline 1,4-dioxide (0.80 g, 2,70 mmol) in chloroform (10 mL). The resulting mixture was stirred at room temperature for 12 h. After washing with aqueous sodium bicarbonate solution, the organic layer was dried over sodium sulfate. After removal of the solvent the residue was chromatographied by eluting with ethyl acetate giving a yellow solid (92%), mp 195-196 °C. IR (KBr): 1371, 1149 cm^{-1}. ^{1}H-NMR (d-chloroform) 3.03 (s, 3H, CH_3); 3.67 (s, 3 H, SO_2CH_3); 8.63 (s, 1 H, H_8); 8.70 (s, 1 H, H_5). MS (EI) m/e (70 eV) M^+= 322. ANAL (calc. for $C_{10}H_6Cl_2N_2O_4S$) C, 37.15; H, 2.48; N, 8.67. Found: C, 37.03; H, 2.54; N, 8.37.

EXAMPLE 58

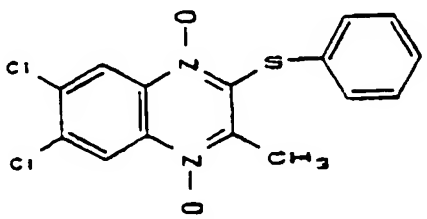
Preparation of 6,7-dichloro-2-methyl-3-(4-nitrophenyl)thioquinoxaline 1,4-dioxide



A mixture of 1-(4-nitrophenyl)thiopropanone (1.40 g, 6.70 mmol), 5,6-dichlorobenzofuroxane (1.40 g, 6.80 mmol) and methanol (10 mL) was bubbled with dry ammonia for 10 min. The complete mixture was allowed to stand at room temperature for 12 h. The precipitate was washed with methanol and recrystallized from methanol-chloroform (30%), mp 192-193 °C. IR (KBr): 3095, 1604, 1338 cm^{-1}. ^{1}H-NMR (d-chloroform) 2.88 (s, 3H, CH_3); 7.30 (d, 2 H, $H_{2'}$ $H_{6'}$, J= 8 Hz); 8.12 (d, 2 H, $H_{3'}$ $H_{5'}$, J= 8 Hz); 8.55 (s, 1 H, H_5); 8.72 (s, 1 H, H_8). MS (EI) m/e (70 eV) M^+= 397. ANAL (calc. for $C_{15}H_9Cl_2N_3O_4S$) C, 45.23; H, 2.26; N, 10.55. Found: C, 45.34; H, 2.44; N, 10.14.

EXAMPLE 59

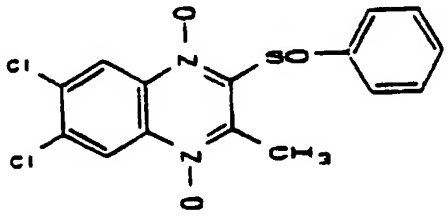
Preparation of 6,7-dichloro-2-methyl-3-phenylthioquinoxaline 1,4-dioxide



Dry ammonia was bubbled into a solution of 1-phenylthiopropanone (7.50 g, 45.20 mmol) and 5,6-dichlorobenzofuroxane (9.30 g, 45.40 mmol) in methanol for 10 min. The mixture was allowed to stand at room temperature for 12 h. The resulting precipitate was filtered and recrystallized from methanol-chloroform (60%), mp 181-182 °C. IR (KBr): 3095, 1600, 1380 cm^{-1}. ^{1}H-NMR (d-chloroform) 2.76 (s, 3H, CH_3); 7.26 (m, 5 H, Ph); 8.55 (s, 1 H, H_8); 8.65 (s, 1 H, H_5). MS (EI) m/e (70 eV) M^+= 352. ANAL (calc. for $C_{15}H_{10}Cl_2N_2O_2S$) C, 50.99; H, 2.83; N, 7.93. Found: C, 51.00; H, 2.87; N, 7.90.

EXAMPLE 60

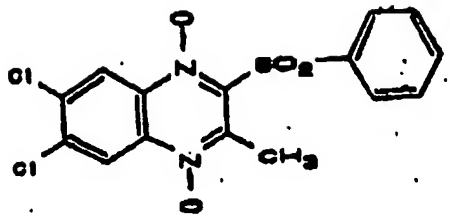
Preparation of 6,7-dichloro-2-methyl-3-phenylsulfinilquinoxaline 1,4-dioxide



A mixture of 6,7-dichloro-2-methyl-3-phenylthioquinoxaline 1,4-dioxide (1.00 g, 2.80 mmol), 3-chloroperbenzoic acid (0.60 g, 3.50 mmol) and chloroform (15 mL) was stirred at room temperature for 12 h. The organic solution was washed with aqueous sodium bicarbonate solution and dried over sodium sulfate. After removal of the solvent, a yellow solid was obtained and recrystallized from methanol-chloroform (78%), mp 161-162 °C. IR (KBr): 3095, 1610, 1329, 1053 cm^{-1}. ^{1}H-NMR (d-chloroform) 2.86 (s, 3H, CH_3); 7.44 (m, 3 H, H_3, H_4, H_5, Ph); 7.95 (m, 2 H, H_2, H_6, Ph); 8.56 (s, 1 H, H_5); 8.65 (s, 1 H, H_8). MS (EI) m/e (70 eV) M^+= 368. ANAL (calc. for $C_{15}H_{10}Cl_2N_2O_3S$) C, 48.78; H, 2.71; N, 7.59. Found: C, 48.50; H, 2.68; N, 7.70.

EXAMPLE 61

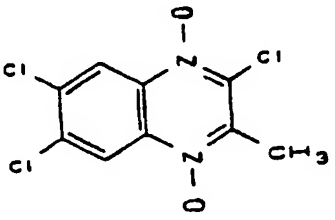
Preparation of 6,7-dichloro-2-methyl-3-phenylsulfonilquinoxaline 1,4-dioxide



A solution of 6,7-dichloro-2-methyl-3-phenylthioquinoxaline 1,4-dioxide (1.00 g, 2.80 mmol) and 3-chloroperbenzoic acid (2.30 g, 13.30 mmol) in chloroform (80 mL) was stirred at room temperature for 12 h. The organic solution was washed with aqueous sodium bicarbonate and dried over sodium sulfate. The solvent was removed and the resulting solid was recrystallized from methanol-chloroform (85%), mp 172-173 °C. IR (KBr): 3090, 1356, 1128 cm^{-1}. ^{1}H-NMR (d-chloroform) 2.54 (s, 3H, CH_3); 7.50 (t, 2 H, H_3, H_5, Ph, J= 8 Hz); 7.69 (t, 1 H, H_4, Ph, J= 8 Hz); 8.08 (d, 2 H, H_2, H_6, Ph, J= 8 Hz); 8.17 (s, 1 H, H_5); 8.49 (s, 1 H, H_8). MS (EI) m/e (70 eV) M^+= 384. ANAL (calc. for $C_{15}H_{10}Cl_2N_2O_4S$) C, 46.75; H, 2.60; N, 7.27. Found: C, 46.61; H, 2.20; N, 6.95.

EXAMPLE 62

Preparation of 2,6,7-trichloro-3-methylquinoxaline 1,4-dioxide

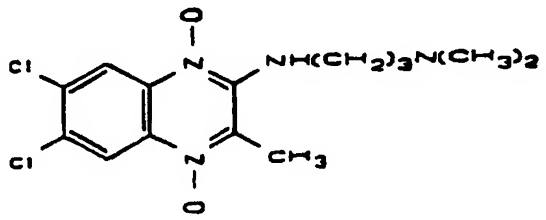


A solution of 6,7-dichloro-2-methyl-3-methylsulfonylquinoxaline 1,4-dioxide (0.50 g, 1.50 mmol) in concentrated HCl (4 mL) was stirred and heated at 80 °C for 30 min. The mixture was stirred at room temperature for 12 h. Addition of water (20 mL) gave a precipitate, which was filtrated and recrystallized from methanol-chloroform giving a yellow solid (24%), mp 175-176 °C. IR (KBr): 1595, 1380 cm^{-1}. ^{1}H-NMR (d-chloroform) 2.82 (s, 3H, CH_3); 8.73 (s, 2 H, H_5 H_8). MS (EI) m/e (70 eV) M^+= 278.

ANAL (calc. for $C_9H_5Cl_3N_2O_2$) C, 38.64; H, 1.79; N, 10.02. Found: C, 38.85; H, 1.78; N, 10.07.

EXAMPLE 63

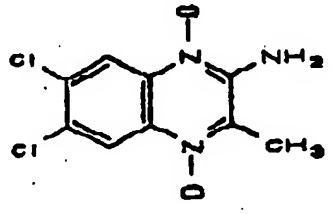
Preparation of 6,7-dichloro-3-methyl-2-[3-(N,N-dimethylamino)propylamino]quinoxaline 1,4-dioxide



[3-(N,N-Dimethylamino)propyl]amine (0.13 g, 1.30 mmol) was added dropwise over a solution of 6,7-dichloro-2-methyl-3-methylsulfonylquinoxaline 1,4-dioxide (0.50 g, 1.50 mmol) in dioxane-chloroform (10 mL-3 mL). The complete mixture was stirred and heated at 80 °C for 10 h. After removal of the solvent an oil was obtained and chromatographied by eluting with dichloromethane-methanol (90/10, v/v) giving a brown-red solid (47%), mp 186-187 °C. IR (KBr): 3440, 1629, 1370 cm^{-1}. ^{1}H-NMR (d-chloroform) 1.88 (q, 2 H, CH_2, J= 6 Hz); 2.25 (s, 6 H, $N(CH_3)_2$); 2.44-2.52 (m, 2 H, CH_2N); 2.73 (s, 3H, CH_3); 3.66 (t, 2 H, NCH_2, J= 6 Hz); 7.69 (s, 1 H, NH); 8.50 (s, 1 H, H_8); 8.54 (s, 1 H, H_5). MS (EI) m/e (70 eV) M^+= 344. ANAL (calc. for $C_{14}H_{18}Cl_2N_4O_2$) C, 48.70; H, 5.22; N, 16.23. Found: C, 48.61; H, 5.34; N, 16.03.

EXAMPLE 64

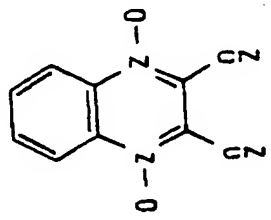
Preparation of 2-amino-6,7-dichloro-3-methylquinoxaline 1,4-dioxide



A solution of 6,7-dichloro-2-methyl-3-methylthioquinoxaline 1,4-dioxide (0.50 g, 1.70 mmol) and formamidine acetate (0.60 g, 5.80 mmol) in 2-ethoxyethanol (6 mL) was heated under reflux for 30 min. Addition of water (10 mL) and subsequent removal of the solvent afforded and oil which was chromatographied by eluting with dichlorometane/methanol (10/90) giving a yellow solid (30%), mp 235-236 °C. IR (KBr): 3413, 3327, 1344 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6) 2.54 (s, 3 H, CH_3); 7.84 (s, 2 H, NH_2); 8.41 (s, 1 H, H_8); 8.48 (s, 1 H, H_5). MS (EI) m/e (70 eV) M^+= 259. ANAL (calc. for $C_9H_7Cl_2N_3O_2$) C, 41.54; H, 2.69; N, 16.15. Found: C, 41.62; H, 2.68; N, 16.24.

EXAMPLE 65

Preparation of 2,3-dicyanoquinoxaline 1,4-dioxide



A) Preparation of quinoxaline 1,4-dioxide

A mixture of benzofuroxane (4.08 g, 30.00 mmol), N,N-diethylamine (2.19 g, 30.00 mmol) and ethyl acetate (15 mL) was stirred at 0 °C for 10 min. Vinyl acetate (5.16 g, 60.00 mmol) was dissolved in ethyl acetate (5 mL) was added and the complete mixture was stirred at room temperature for 72 h. After removal of the solvent, the crude solid was recrystallized from isopropanol giving a yellow solid (79%), mp 240- 241 °C.

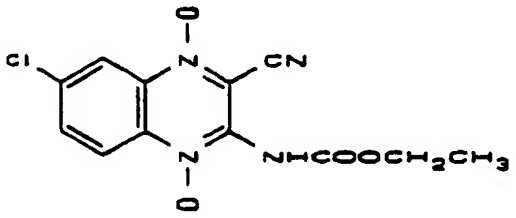
This compound was used without further purification.

B) A mixture of quinoxaline 1,4-dioxide (1.00 g, 6.20 mmol), potassium ferricyanide (2.44 g, 7.40 mmol), potassium cyanide (2.44 g, 30.10 mmol), ethanol (70 mL) and

water (30 mL) was stirred at 0 °C for 3 h. The precipitate was filtrated and purified by chromatography by eluting with ethyl acetate. Yellow solid (18%), mp 224 °C. IR (KBr): 2236, 1365 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6) 8.24-8.29 (m, 2 H, H_6 H_7); 8.59-8.63 (m, 2 H, H_5 H_8). MS (EI) m/e (70 eV) M^+= 212. ANAL (calc. for $C_{10}H_4N_4O_2$) C, 56.60; H, 1.89; N, 26.41. Found: C, 56.36; H, 1.91; N, 26.42.

EXAMPLE 66

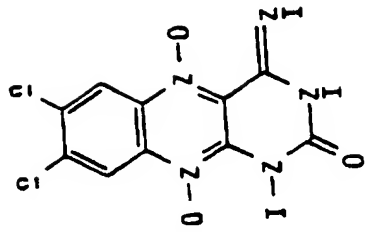
Preparation of 7-chloro-3-ethoxycarbonylamino-2-quinoxalinecarbonitrile 1,4-dioxide



A solution of 7-chloro-4-cyano-2-oxo-1,2,4-oxadiazolo[2,3-a]quinoxaline 5-oxide (0.50 g, 1.90 mmol) in methanol (25 mL) was heated under reflux for 2 h. The precipitate was filtrated and washed with ethyl ether and recrystallized from ethanol/dioxane (17%), mp 178 °C. IR (KBr): 3414, 1724, 1531, 1323 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6): 1.27 (t, 3 H, CH_3); 4.22 (c, 2 H, CH_2); 8.09 (d, 1 H, H_6); 8.46 (d, 1 H, H_5); 8.49 (s, 1 H, H_8). MS (EI) m/e (70 eV) M^+= 308. ANAL (calc. for $C_{12}H_9ClN_4O_4$) C, 46.68; H, 2.92; N, 18.15. Found: C, 46.55; H, 2.88; N, 17.98.

EXAMPLE 67

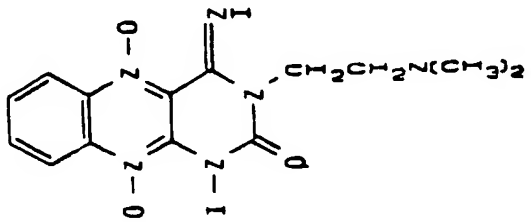
Preparation of 7,8-dichloro-4-iminobenzopteridine 5,10-dioxide



Chloroform (20 mL) was saturated with dry ammonia and 7,8-dichloro-2-oxo-1,2,4-oxadiazolo[2,3-a]quinoxaline 5-oxide (0.15 g, 0.51 mmol) was added. The dark red solution was stirred for 10 h. The resulting precipitate was filtered and washed with hot acetone and diethyl ether. (56%), mp >300 °C. IR (KBr): 3451, 3090, 1696, 1546, 1435 cm^{-1}. ^{1}H-NMR (TFA): 8.88 (s, 1 H, H_6); 8.97 (s, 1 H, H_9). MS (EI) m/e (70 eV) M^+-16= 298. ANAL (calc. for $C_{10}H_5Cl_2N_5O_3$) C, 38.22; H, 1.59; N, 22.29. Found: C, 38.28; H, 2.14; N, 22.27.

EXAMPLE 68

Preparation of 4-imino-3-[2-(N,N-dimethylamino)ethyl]benzopteridine 5,10-dioxide



A solution of 4-cyano-2-oxo-1,2,4-oxadiazolo[2,3-a]quinoxaline 5-oxide (0.20 g, 0.87 mmol) in dry dichloromethane (20 mL) was stirred for 30 min. 2-(N,N-dimethylamino)ethylamine (5 drops) was added and the solution turned red. The mixture was allowed to stand at room temperature for 18 h. The purple solid was filtrated in vacuo and washed with light petroleum ether (70%), mp 222 °C. IR (KBr): 3412, 1609, 1581, 1447 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6): 3.02 (s, 6 H, 2 CH_3); 3.41 (m, 4 H, 2 CH_2); 7.30 (t, 1 H, H_7); 7.51 (d, 1 H, H_6); 7.69 (t, 1 H, H_8); 8.13 (d, 1 H, H_9); 11.42 (s, 1 H, NH). MS (EI) m/e (70 eV) M^+- 16= 300. ANAL (calc. for $C_{14}H_{16}N_6O_3$) C, 53.16; H, 5.06; N, 26.58. Found: C, 52.85; H, 5.36; N, 26.41.

Cytotoxicity assays

The cytotoxicity assays were carried out in V79 cells (Chinese hamster lung fibroblasts) obtained from the ATCC. They were grown as monolayers in EMEM 10% FBS at 37°C and 5% CO_2. Cells from exponentially growing cultures were trypsinized and a suspension of $2x10^4$ cells/ ml was prepared. 30 ml of this suspension were dispensed into 50 ml glass flasks, which were hermetically sealed with rubber caps. Cells were maintained in suspension at 37°C and the flasks were gassed either with pure air or with pure Nitrogen. After thirty minutes, the compounds were added and the cells were gassed for a further two hours in the presence of the compound. At the end of the 2 hours the cells were washed and resuspended in fresh medium, they were counted and various numbers were cloned into plastic dishes. After seven days of growth at 37°C and 5% CO_2, the clones were fixed and stained. Clones with more than 64 cells (equivalent to six cell divisions) were counted and the plating efficiency calculated. The surviving percentage in air and hypoxia was calculated by dividing the plating efficiency of the compound treated cells by that of the solvent treated control cells.

Compounds were tested twice in oxic and hypoxic conditions and the potency and hypoxia selectivity of the compounds were determined from dose-response graphs. The potency is the dose which kills 99% of hypoxic cells; the lower the value, the greater the compound potency. The selectivity is determined by the Hypoxic Cytotoxicity Ratio (HCR), that is the dose in air divided by the dose in hypoxia giving the same level of cell killing. The higher the HCR, the greater the hypoxia selectivity.

In the Figure 1 the percentage of surviving cells after treatment in air or hypoxia with 2-quinoxalinecarbonitrile 1,4-dioxide (Example 13, Fig. 1A) and 6(7)-chloro-3-[3-(N,N-dimethylamino) propylamino]-2-quinoxalinecarbonitrile 1,4-dioxide (Example 27, Fig. 1B), are shown. In hypoxia, 0.4 μM of compound 27 kills 99% of the cells (Potency = 0.4), under oxic conditions, a 250 fold greater concentration is needed

to obtain the same percentage of cell killing (HCR = 250). Under the same assay conditions the potency and HCR for Tirapazamine are 30 and 75, respectively. Thus compound 27 is 75 times more potent and 3 times more selective than Tirapazamine.

In Table I the potency and HCR of several quinoxalines are shown, all these quinoxalines are more potent than Tirapazamine and most of them are also more selective.

TABLE I

COMPOUND	Potency	HCR	COMPOUND	Potency	HCR
Example 1	9	200	Example 28	1	300
Example 2	1	80	Example 29	2	200
Example 5	15	100	Example 30	0.6	170
Example 6	7	75	Example 31	0.3	340
Example 9	4	8	Example 32	0.9	120
Example 10	15	50	Example 33	0.5	40
Example 13	5	>100	Example 34	3	100
Example 14	3	30	Example 35	1	102
Example 15	0.7	10	Example 36	0.4	75
Example 16	6	200	Ex. 38 (6-Cl)	0.8	>125
Example 17	5	>200	Ex. 38 (7-Cl)	2	300
Ex. 18 (7-Cl)	6	80	Example 40	0.7	10
Example 19	0.2	200	Example 43	0.3	30
Example 26	1	300	Example 67	5	>12
Example 27	0.4	250	Tirapazamine	30	75

Determination of MTD

The maximum tolerated dose (MTD) was determined in female Balb/C mice of 20-25g weight. The MTD was determined after a single i.p. administration and was defined as the dose which produces a 20% weight loss on the third day after dosing. In Table II some MTD data are presented. All the compounds were prepared

immediately before the injection. The 3-amino-2-quinoxalinecarbonitrile 1,4-dioxides (1, 2, 5 and 6) and Tirapazamine were suspended in Tween 80 90%/ saline 10%. All of these quinoxalines are less toxic than Tirapazamine. 7-chloro-3-[3-(N,N-dimethylamino)propylamino]-2-quinoxalinecarbonitrile 1,4-dioxide (27) was dissolved in saline. This compound is five times more toxic than Tirapazamine.

TABLE II

COMPOUND	MTD (mMols/kg)	MTD (mg/kg)
Example 1	0.6	142
Example 2	0.8	217
Example 5	0.6	176
Example 6	0.5	135
Example 27	0.06	25.8
Tirapazamine	0.3	53.4

Solubility of compound 27

In tests run in parallel on Tirapazamine and compound 27, the latter was at least 10 times more soluble than the former, although saturation was not achieved with compound 27.

COMPOUND	SOLUBILITY
Tirapazamine	$6,7 \times 10^{-3}$ M
Example 27	$> 6,7 \times 10^{-2}$ M

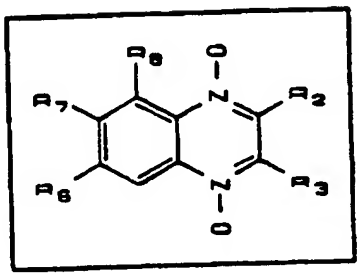
In vivo activity of compound 27

Compound 27 was tested on EMT-6 mouse mammary tumours in an *ex vivo* cloning assay. It was administered in combination with radiation, so that the radiation would kill well oxygenated cells, allowing the effect of the compound on hypoxic cells to be measured. Briefly, 2×10^6 EMT-6 cells were innoculated subcutaneously in the right side of female Balb/C mice. When the tumours reached approximately 7mm in diameter the treatment began. Mice were dosed i.p. with 0.01 mMole/kg of compound 27 or 0.08 mMole/kg of Tirapazamine, given 30 minutes before each radiation session. The entire animal was irradiated with a dose of 1.5 Gy of 15MeV electrons from a linear accelerator (SIEMENS A.G. Modelo MEVATRON 77), twice a day (0.900h and 18.00h), on four consecutive days. Controls which received only radiation or only saline were also included. 24h after the last treatment, the tumours were removed, chopped mechanically and digested with a mixture of collagenase, pronase and DNAse. After filtering the suspension through a mesh of 35 μm diameter, the cells were centrifuged. Live cells, counted with Trypan blue, were cloned in RPMI 20% FBS . On day seven the clones were stained and counted.

The results are presented in Figure 2. The clonogenic capacity of the irradiated cells was 50% lower than the controls which received only saline. When Tirapazamine and compound 27 were given without radiation, the cloning efficiency was markedly reduced. When compound 27 was given before each radiation dose, an enhancement of the radiation response was observed. The effect was similar to the one obtained with Tirapazamine given at an 8 fold higher dose. Since the MTD of compound 27 is 5-fold lower than that of Tirapazamine, the Therapeutic Index (effective dose:toxic dose) of compound 27 is at least 1.6 times higher than Tirapazamine.

CLAIMS

1. A compound of Formula 1



wherein:

R_2 is hydrogen, cyano or;

R_2 is C1-4alkyl, $-CH_2$-NH-NH-COO-(C1-4alkyl), C1-4alkyloxycarbonyl, C1-4alkylthio, C1-4alkylsulfinyl, C1-4alkilsulfonyl, C2-5alkanoyl, or;

R_2 is a group of formula -CH=CH-CO-R9 wherein R9 is C1-6alkyl or phenil and phenil may be optionally replaced by 1 or 2 substituents chosen between halogen anc C1-4alcoxi or,

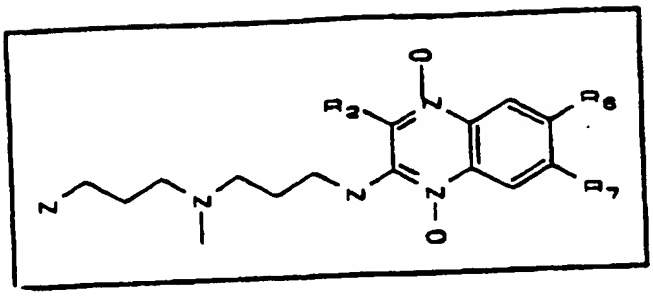
R_2 is a group of formula -C(R10)=N-NH-R11 wherein R10 is H or C1-4alkyl and R11 is a group of formula -X-Y wherein X can be a simple link, carbonyl, thiocarbonil, thiol, sulfinyl and sulfonyl and Y can be amino and phenyl where phenyl can be optionally replaced by one or two substituents chosen between NO_2, amino and methyl

R_3 is a group of formula

-NH-C1-6alkyl-N(A1)(A2)

wherein A1 and A2 are independently H or C1-4alkyl optionally susbtituted the alkyl by hydroxi C1-4 alkoxy, amino, C1-4alkylamino, thiol or C1-4alkylthio or A1 and A2 along with N complete a 5 or 6 membered heterocyclic ring optionally containing a N, O or S atom in lieu of a carbon atom; this ring can optionally have a carbon replaced by C1-4alkyl or

R_3 represents a group of formula



wherein R2 has the meaning defined in claim 1 and R6 and R7 have the meaning defined in claim 1 or R2 and R3 together represent a group of formula -NH-CO-NR11-C(=NH)- wherein R11 independently represents H, C1-4alkyl or C1-4alkyl-N(R12,R13) wherein R12 and R13 independently represent H or C1-4alkyl

R_6 and R_7 independently represent

H;

halogen;

CF_3;

C1-4alkyl;

C2-5alkanoylamino;

cyano;

phenyl optionally substituted with 1-2 substituents selected from NO_2 and C(1-4)alkyl;

R_8 represents H or NO_2;

with the exception of 1,4-dioxide 2-(3-dimethylamino-propylamino)-quinoxaline which is excluded

or a pharmaceutically acceptable salt derived.

2. A compound according to claim 1 wherein R_2 is cyano.

3. A compound as claims 1 or 2 wherein R6 and R7 independently represent H, Cl, MeO or CF_3 if R6 or R7 are not hydrogen

4. A compound as claims 1-3 wherein R8 is H.

5. A compound as claims 1-4 wherein R3 is a group of formula -NH-C1-6alkyl-N(A1)(A2)

wherein A1 and A2 are independently H or C1-4alkyl optionally replaced the alkyl by hydroxy, C1-4 alkoxy, amino, C1-4alkylamino, thiol or C1-4alkylthio or

A1 and A2 along with N complete a 5 or 6 membered heterocyclic ring optionally containing a N, O or S atom in lieu of a carbon atom; this ring can optionally have a carbon replaced by C1-4alkyl or

6. Any of the following compounds:
6-fluoro-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
6-trifluoromethyl-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
6-methoxy-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
6-fluoro-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
6-trifluoromethyl-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
6-methoxy-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
6-chloro-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
7-fluoro-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
7-trifluoromethyl-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
7-methoxy-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
7-fluoro-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
7- trifluoromethyl-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
7-methoxy-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
7-chloro-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide

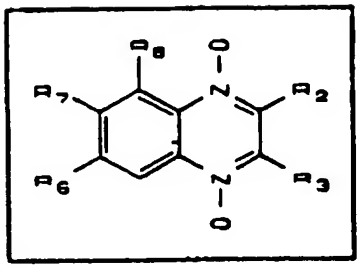
or a mixture of isomers in position 6 and 7 or a pharmaceutically acceptable salt derivated from them.

7. Any of the following compounds:
6(7)-chloro-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
7-chloro-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
6-chloro-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide

or a pharmaceutically acceptable salt derivated from them.

8. A compound of:

Formula 1



wherein

R2 is defined in claim 1

R3 is H

amino optionally mono- or di-substituted by C1-alkyloxicarbonyl; C2-5alkanoylamine optionally substituted the carbon by hydrogen, phenylthio, phenylsulphynil or phenylsulphonyl optionally mono- di- or tri-substitued the phenyl by halogen or NO_2 or,

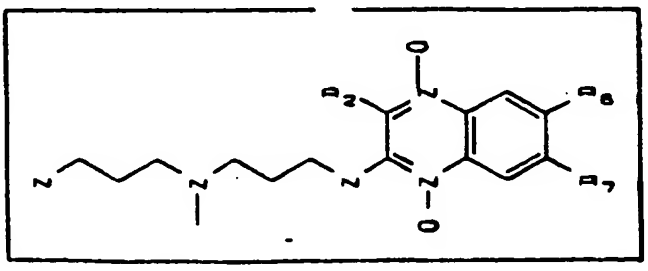
R3 is a group of the formula

-NH-C1-6alkyl-N(A1)(A2)

wherein A1 and A2 are independently H or C1-4alkyl optionally replaced the alkyl by hydroxy, C1-4 alkoxy, amino, C1-4alkylamino, thiol or C1-4alkylthio or

A1 and A2 along with N complete a 5 or 6 membered heterocyclic ring optionally containing a N, O or S atom in lieu of a carbon atom; this ring can optionally have a carbon replaced by C1-4alkyl or

R3 represents a group of formula

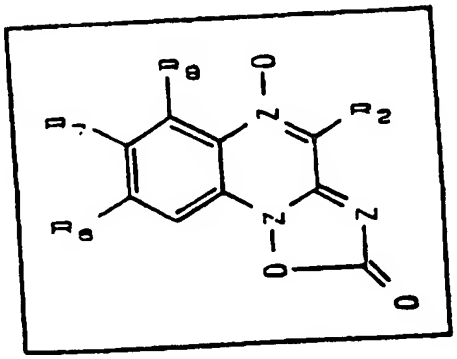


R2, R6 and R7 have the meaning defined in claim 1 or R2 and R3 together represent a group of formula
-NH-CO-NR11-C(=NH)- wherein R11 independently represents H, C1-4alkyl or C1-4alkyl-N(R12,R13) wherein R12 and R13 independently represent H or C1-4alkyl or

R3 represents
cyano
C2-6alkanoylamino
C2-6alkanoyl
C1-4alkylthio
C1-4alkylsulfinyl
C1-4alkylsulfonyl
C1-4alkyloxycarbonyl
halogen
C1-6alkyl or
a group of formula
-NH-CO-Het
wherein Het is a heterociclyc complete a 5 or 6 membered heterocyclic ring containing an O or S atom

C1-4alkylsulfonylamino
C1-4alkylsulfinylamino
C1-4alkylthyoamino
C1-6alkylamino

R6 y R7 are defined in the claim 1
R8 represents H or NO_2 or
a compound of the formula 2



wherein R2, R6, R7 y R8 are defined in claim 1 or a or a pharmaceutically acceptable salt derivated from them for use in killing selectively hypoxic tumoral cells in a mammal.

9. A compound as claim 8 wherein R2 is cyano

10. A compound as claims 8 or 9 wherein R6 and R7 independently represent H, Cl, F, MeO or CF_3 unless R6 or R7 is not hydrogen.

11. A compound as claims 8-10 wherein R8 is H.

12. A compound as claims 8-11 wherein R3 is a group of formula

-NH-C1-6alkyl-N(A1)(A2)

wherein A1 and A2 are independently H or C1-4alkyl optionally replaced the alkyl by hydroxy, C1-4 alkoxy, amino, C1-4alkylamino, thiol or C1-4alkylthio or

A1 and A2 along with N complete a 5 or 6 membered heterocyclic ring optionally containing a N, O or S atom in lieu of a carbon atom; this ring can optionally have a carbon replaced by C1-4alkyl

13. A compound as claim 8 where the compound is any of the following:

6-fluoro-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide

6-trifluoromethyl-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide

6-methoxy-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide

6-fluoro-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide

6-trifluoromethyl-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide

6-methoxy-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide

6-chloro-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide

7-fluoro-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide

7-trifluoromethyl-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide

7-methoxy-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide

7-fluoro-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide

7- trifluoromethyl-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
7-methoxy-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
7-chloro-3-(3-dimethylamino-ethylamino)-2-quinoxalinecarbonitrile 1,4-dioxide

or a mixture of isomers in position 6 and 7 or a pharmaceutically acceptable salt derivated from them.

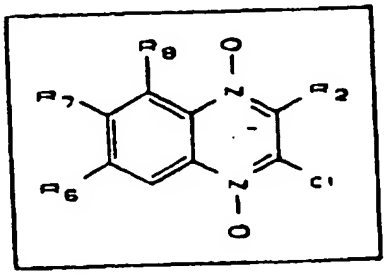
14. A compound as claim 8 where the compound is one of the following:
6(7)-chloro-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
7-chloro-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide
6-chloro-3-(3-dimethylamino-propylamino)-2-quinoxalinecarbonitrile 1,4-dioxide

or a pharmaceutically acceptable salt derivated from them.

15. Use of a compound as defined in any of claims 8-14 as medicine

16. Use of a compound as defined in any of claims 8-14 in the preparation of a medicine to selectively kill hypoxic tumoral cells in a mammal.

17 A proccess for preparation of compounds defined in claim 1 that includes the reaction of a formula 3 compound

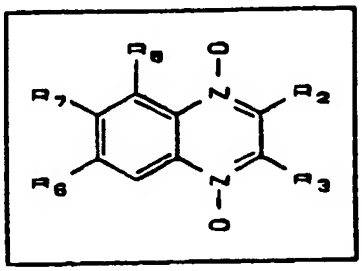


wherein R2, R6 and R7 have a meaning defined in claim 1 with a compound with a formula

NH2-C1-6alkyl-N(A1)(A2)

wherein A1 and A2 have a meaning defined in claim 1 in relation with the radical R3, in presence of a polar aprotic solvent and if desired converting the compound thus obtained in a salt.

18. A compound of Formula 1

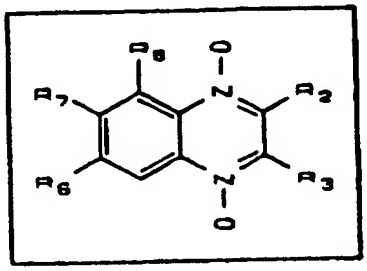


Substantially as hereinbefore described with reference to any one of the Examples.

19. A compound as defined in claim 8 for use substantially as hereinbefore described.

20. Use of a compound as defined in claim 8 substantially as hereinbefore described.

21. A process for the preparation of compounds of Formula 1



substantially as hereinbefore described with reference to any one of the Examples.

The Patent Office

96

Application No: GB 9600963.4 **Examiner:** Peter Davey
Claims searched: 1-21 **Date of search:** 17 April 1996

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): C2C (CLY, CLZ)

Int Cl (Ed.6): C07D 241/52

Other: Online: WPI, CAS ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
P,X	Chemical Abstracts 124:55903	8 at least
P,X	Chemical Abstracts 123:340002	8 at least
P,X	Chemical Abstracts 123:265	8 at least

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.